UTILITY APPLICATION

UNDER 37 CFR § 1.53(B)

TITLE: **TRICYCLIC ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS**

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Utility Application Transmittal Sheet (1 pg); Description (109 pgs); Claims (32 pgs); Abstract (1 pg); and Return Postcard

PRIORITY DATA: Under U.S.C. 119(e)(1) this application claims the benefit of U.S. Provisional Patent Application Serial 60/271,189, filed February 23, 2001.

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Dorothy Chambers

TRICYCLIC ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS

Related Application

The present application claims the benefit of priority to U.S. Provisional Application No. 60/271,189, filed on February 23, 2001 which is incorporated by reference in its entirety.

Field of the Invention

This invention relates to non-steroidal compounds that are modulators (*i.e.* agonists, partial agonists and antagonists) of androgen receptors and to methods for making and using such compounds.

Background of the Invention

Intracellular receptors (IRs) form a class of structurally-related genetic regulators scientists have named "ligand dependent transcription factors" (R. M. Evans, *Science*, 240:889, 1988). Sex steroid hormone receptors are a recognized subset of the IRs, including androgen receptor (AR), progesterone receptor (PR) and estrogen receptor (ER). Regulation of a gene by such factors requires both the receptor itself and a corresponding ligand, which has the ability to selectively bind to the receptor in a way that affects gene transcription.

The natural hormones for sex steroid receptors have been known for a long time, such as testosterone for AR and progesterone for PR. A compound that binds to a receptor and mimics the effect of the native hormone is referred to as an "agonist", while a compound that inhibits the effect of the native hormone is called an "antagonist." The term "modulators" refers to compounds that are agonists, partial agonists or antagonists.

Synthetic female sex hormones have been widely used in oral contraception, hormone replacement therapy and the treatment of hormone-dependent disorders. The development of new generations of selective estrogen receptor modulators (SERMs) significantly improved women's health. On the other hand, similar hormone therapy for men has not been fully explored due to lack of availability of selective, orally administered, safe agents.

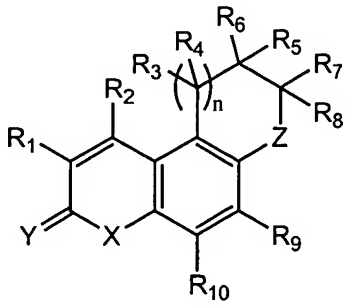
A group of hydroquinoline derivatives was recently described as AR modulators (*e.g.*, U.S. Patent No. 5,696,130). This group of AR modulators was developed by using cell-based high-throughput assays, termed cotransfection assays.

The entire disclosures of the publications and references referred to herein are incorporated by reference herein and are not admitted to be prior art.

Summary of the Invention

The present invention is directed to tricyclic androgen receptor modulator compounds. This invention is also directed to pharmaceutical compositions containing such compounds as well as methods of using such compounds and pharmaceutical compositions for modulating processes mediated by androgen receptor (AR). More particularly, the invention relates to nonsteroidal compounds and compositions that may be high affinity, high specificity agonists, partial agonists (*i.e.*, partial activators and/or tissue-specific activators) or antagonists for androgen receptor. Also provided are methods of making such compounds and pharmaceutical compositions, as well as intermediates used in their synthesis.

The present invention provides a novel class of AR modulator compounds of the formula:



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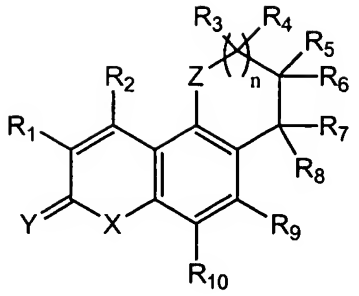

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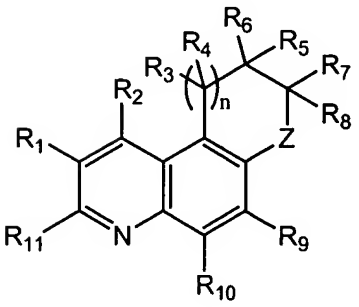

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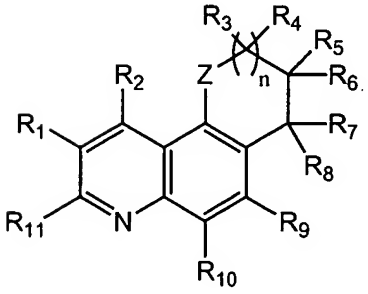

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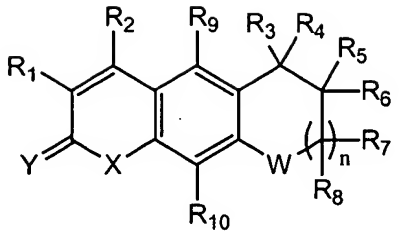

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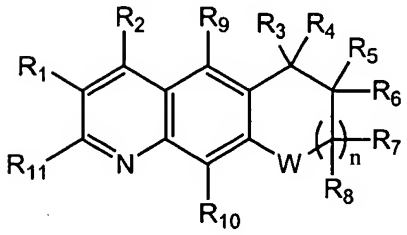

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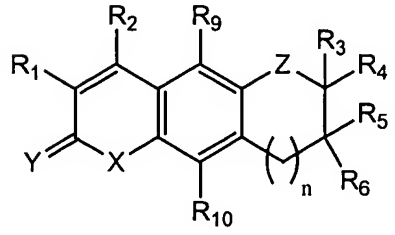

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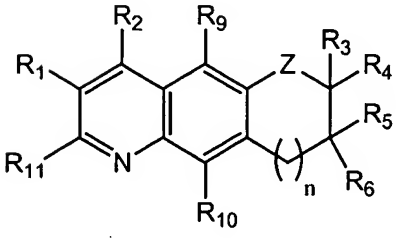


(VIII)

wherein:

R^1 is selected from the group of hydrogen, F, Cl, Br, I, NO_2, OR^{12}, SR^{12}, SOR^{12}, SO_2R^{12}, $NR^{12}R^{13}$, C_1-C_8 alkyl, C_1-C_8 haloalkyl and C_1-C_8 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted;

R^2 is selected from the group of hydrogen, F, Cl, Br, I, CH_3, CF_3, CHF_2, CH_2F, CF_2Cl, CN, CF_2OR^{12}, CH_2OR^{12}, OR^{12}, SR^{12}, SOR^{12}, SO_2R^{12}, $NR^{12}R^{13}$, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 heteroalkyl, C_2-C_8 alkenyl and C_2-C_8 alkynyl, wherein the alkyl, haloalkyl, heteroalkyl, alkenyl and alkynyl groups may be optionally substituted;

R^3 through R^8 each independently is selected from the group of hydrogen, F, Cl, Br, I, OR^{12}, $NR^{12}R^{13}$, SR^{12}, SOR^{12}, SO_2R^{12}, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 heteroalkyl, C_2-C_8 alkynyl, C_2-C_8 alkenyl, aryl, heteroaryl and arylalkyl, wherein the alkyl, haloalkyl, heteroalkyl, alkynyl, alkenyl, aryl, heteroaryl and arylalkyl groups may be optionally substituted; or

R^3 and R^5 taken together form a bond; or

R^5 and R^7 taken together form a bond; or

R^4 and R^6 taken together form a three- to eight-membered saturated or unsaturated carbocyclic or heterocyclic ring, wherein the carbocyclic or heterocyclic ring may optionally substituted; or

R^6 and R^8 taken together form a three- to eight-membered saturated or unsaturated carbocyclic or heterocyclic ring, wherein the carbocyclic or heterocyclic ring may optionally substituted;

R^9 and R^{10} each independently is selected from the group of hydrogen, F, Cl, Br, I, CN, OR^{12}, $NR^{12}R^{13}$, $C_m(R^{12})_{2m}OR^{13}$, SR^{12}, SOR^{12}, SO_2R^{12}, $NR^{12}C(O)R^{13}$, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 heteroalkyl and arylalkyl, wherein the alkyl, haloalkyl, heteroalkyl and arylalkyl groups may be optionally substituted;

R^{11} is selected from the group of hydrogen, F, Br, Cl, I, CN, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 heteroalkyl, OR^{14}, $NR^{14}R^{13}$, SR^{14}, CH_2R^{14}, $C(O)R^{14}$, CO_2R^{14}, $C(O)NR^{14}R^{13}$,

SOR^{14} and SO_2R^{14}, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted;

R^{12} and R^{13} each independently is selected from the group of hydrogen, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, heteroaryl and aryl, wherein the alkyl, haloalkyl, heteroalkyl, alkenyl, alkynyl, heteroaryl and aryl groups may be optionally substituted;

R^{14} is selected from the group of hydrogen, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 heteroalkyl, aryl, heteroaryl, $C(O)R^{15}$, CO_2R^{15} and $C(O)NR^{15}R^{16}$, wherein the alkyl, haloalkyl, heteroalkyl, aryl and heteroaryl groups may be optionally substituted;

R^{15} and R^{16} each independently is selected from the group of hydrogen, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted;

W is O or S;

X is selected from the group of O, S and $N\{R^{14}\}$;

Y is selected from the group of O, S, $N\{R^{12}\}$, $N\{OR^{12}\}$ and $CR^{12}R^{13}$;

Z is selected from the group of O, S and $N\{R^{12}\}$;

n is 0, 1 or 2;

m is 0, 1, or 2;

and pharmaceutically acceptable salts thereof.

Detailed Description of the Invention

In accordance with the present invention and as used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

The term "alkyl," alone or in combination, refers to an optionally substituted straight-chain or branched-chain alkyl radical having from 1 to about 12 carbon atoms. The term also includes substituted straight-chain or branched-chain alkyl radicals having from 1 to about 6 carbon atoms as well as those having from 1 to about 4 carbon atoms. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, tert-

amyl, pentyl, hexyl, heptyl, octyl and the like.

The term "alkenyl," alone or in combination, refers to an optionally substituted straight-chain or branched-chain hydrocarbon radical having one or more carbon-carbon double-bonds and having from 2 to about 18 carbon atoms. The term also includes substituted straight-chain or branched-chain hydrocarbon radicals having one or more carbon-carbon double bonds and having from 2 to about 6 carbon atoms as well as those having from 2 to about 4 carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, butenyl, 1,4-butadienyl and the like.

The term "alkynyl," alone or in combination, refers to an optionally substituted straight-chain or branched-chain hydrocarbon radical having one or more carbon-carbon triple-bonds and having from 2 to about 12 carbon atoms. The term also includes substituted straight-chain or branched-chain hydrocarbon radicals having one or more carbon-carbon triple bonds and having from 2 to about 6 carbon atoms as well as those having from 2 to about 4 carbon atoms. Examples of alkynyl radicals include ethynyl, propynyl, butynyl and the like.

The term "heteroalkyl" refers to alkyl groups, as described above, in which one or more skeletal atoms are oxygen, nitrogen, sulfur or combinations thereof. The term heteroalkyl also includes alkyl groups in which one 1 to about 6 skeletal atoms are oxygen, nitrogen, sulfur or combinations thereof, as well as those in which 1 to 4 skeletal atoms are oxygen, nitrogen, sulfur or combinations thereof and those in which 1 to 2 skeletal atoms are oxygen, nitrogen, sulfur or combinations thereof.

The term "alkoxy," alone or in combination, refers to an alkyl ether radical, alkyl-O-, wherein the term alkyl is defined as above. Examples of alkoxy radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and the like.

The term "aryloxy," alone or in combination, refers to an aryl ether radical wherein the term aryl is defined as below. Examples of aryloxy radicals include phenoxy, benzyloxy and the like.

The term "alkylthio," alone or in combination, refers to an alkyl thio radical, alkyl-S-, wherein the term alkyl is defined as above.

The term "arylthio," alone or in combination, refers to an aryl thio radical, aryl-S-, wherein the term aryl is defined as below.

The term "oxo" refers to =O.

The term "aryl," alone or in combination, refers to an optionally substituted aromatic ring system. The term aryl includes monocyclic aromatic rings, polyaromatic rings and polycyclic aromatic ring systems containing from six to about twenty carbon atoms. The term aryl also includes monocyclic aromatic rings, polyaromatic rings and polycyclic ring systems containing from 6 to about 12 carbon atoms, as well as those containing from 6 to about 10 carbon atoms. The polyaromatic and polycyclic aromatic rings systems may contain from two to four rings. Examples of aryl groups include, without limitation, phenyl, biphenyl, naphthyl and anthryl ring systems.

The term "heteroaryl" refers to optionally substituted aromatic ring systems containing from about five to about 20 skeletal ring atoms and having one or more heteroatoms such as, for example, oxygen, nitrogen and sulfur. The term heteroaryl also includes optionally substituted aromatic ring systems having from 5 to about 12 skeletal ring atoms, as well as those having from 5 to about 10 skeletal ring atoms. The term heteroaryl may include five- or six-membered heterocyclic rings, polycyclic heteroaromatic ring systems and polyheteroaromatic ring systems where the ring system has two, three or four rings. The terms heterocyclic, polycyclic heteroaromatic and polyheteroaromatic include ring systems containing optionally substituted heteroaromatic rings having more than one heteroatom as described above (*e.g.*, a six membered ring with two nitrogens), including polyheterocyclic ring systems of from two to four rings. The term heteroaryl includes ring systems such as, for example, furanyl, benzofuranyl, chromenyl, pyridyl, pyrrolyl, indolyl, quinolinyl, N-alkyl pyrrolyl, pyridyl-N-oxide, pyrimidoyl, pyrazinyl, imidazolyl, pyrazolyl, oxazolyl, benzothiophenyl, purinyl, indolizinyl, thienyl and the like.

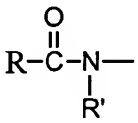
The term "heteroarylalkyl" refers to a C_1-C_4 alkyl group containing a heteroaryl group, each of which may be optionally substituted.

The term "heteroarylthio" refers to the group -S-heteroaryl.

The term "acyloxy" refers to the ester group –OC(O)-R, where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, or arylalkyl, wherein the alkyl, alkenyl, alkynyl and arylalkyl groups may be optionally substituted.

The term "carboxy esters" refers to –C(O)OR where R is alkyl, aryl or arylalkyl, wherein the alkyl, aryl and arylalkyl groups may be optionally substituted.

The term "carboxamido" refers to



where R and R' each independently is selected from the group of hydrogen, alkyl, aryl and arylalkyl, wherein the alkyl, aryl and arylalkyl groups may be optionally substituted.

The term "cycloalkyl", alone or in combination, refers to a monocyclic, bicyclic or tricyclic alkyl radical wherein each cyclic moiety has from 3 to about 8 carbon atoms. Examples of cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

The term "arylalkyl," alone or in combination, refers to an alkyl radical as defined above in which one hydrogen atom is replaced by an aryl radical as defined above, such as, for example, benzyl, 2-phenylethyl and the like.

The terms haloalkyl, haloalkenyl, haloalkynyl and haloalkoxy include alkyl, alkenyl, alkynyl and alkoxy structures, as described above, that are substituted with one or more fluorines, chlorines, bromines or iodines, or with combinations thereof.

The terms cycloalkyl, aryl, arylalkyl, heteroaryl, alkyl, alkynyl, alkenyl, haloalkyl and heteroalkyl include optionally substituted cycloalkyl, aryl, arylalkyl, heteroaryl, alkyl, alkynyl, alkenyl, haloalkyl and heteroalkyl groups.

The term "carbocycle" includes optionally substituted, saturated or unsaturated, three- to eight-membered cyclic structures in which all of the skeletal atoms are carbon.

The term "heterocycle" includes optionally substituted, saturated or unsaturated, three- to eight-membered cyclic structures in which one or more skeletal atoms is oxygen, nitrogen, sulfur, or combinations thereof.

The term "acyl" includes alkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl substituents attached to a compound *via* a carbonyl functionality (*e.g.*, -CO-alkyl, -CO-aryl, -CO-arylalkyl or -CO-heteroarylalkyl, *etc.*).

"Optionally substituted" groups may be substituted or unsubstituted. The substituents of an "optionally substituted" group may include, without limitation, one or more substituents independently selected from the following groups or designated subsets thereof: alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, haloalkenyl, haloalkynyl, cycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxy, aryloxy, haloalkoxy, amino, alkylamino, dialkylamino, alkylthio, arylthio, heteroarylthio, oxo, carboxyesters, carboxamido, acyloxy, hydrogen, F, Cl, Br, I, CN, NO_2, NH_2, N_3, $NHCH_3$, $N(CH_3)_2$, SH, SCH_3, OH, OCH_3, OCF_3, CH_3, CF_3, $C(O)CH_3$, CO_2CH_3, CO_2H, $C(O)NH_2$, OR^9, SR^9 and $NR^{10}R^{11}$. An optionally substituted group may be unsubstituted (e.g., $-CH_2CH_3$), fully substituted (e.g., $-CF_2CF_3$), monosubstituted (e.g., $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and monosubstututed (e.g., $-CH_2CF_3$).

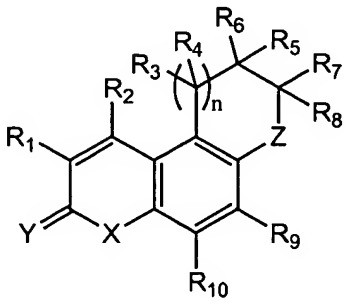
The term "halogen" includes F, Cl, Br and I.

The term "mediate" means affect or influence. Thus, for example, conditions mediated by an androgen receptor are those in which an androgen receptor plays a role. Androgen receptors are known to play a role in conditions including, for example, acne, male-pattern baldness, sexual dysfunction, impotence, wasting diseases, hirsutism, hypogonadism, prostatic hyperplasia, osteoporosis, cancer cachexia, and hormone-dependent cancers.

The term "selective" refers to compounds that display reactivity towards a particular receptor (e.g., an androgen receptor) without displaying substantial cross-reactivity towards another receptor (e.g., glucocorticoid receptor). Thus, for example, selective compounds of the present invention may display reactivity towards androgen receptors without displaying substantial cross-reactivity towards glucocorticoid receptors.

In one embodiment, selective compounds of the present invention display at least 50-fold greater reactivity towards a particular receptor than towards another receptor. In another embodiment, selective compounds of the present invention display at least 100-fold greater reactivity towards a particular receptor than towards another receptor. In yet another embodiment, selective compounds of the present invention display at least 500-fold greater reactivity towards a particular receptor than towards another receptor. In still another embodiment, selective compounds of the present invention display at least 1,000-fold greater reactivity towards a particular receptor than towards another receptor.

Compounds of the present invention may be represented by the formulae:



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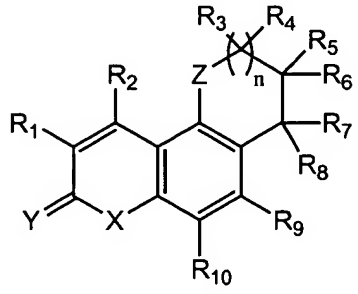

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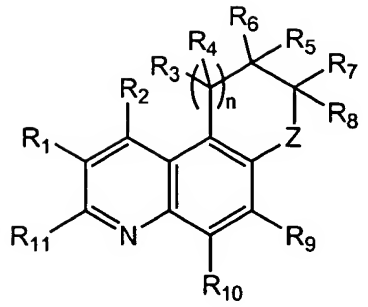

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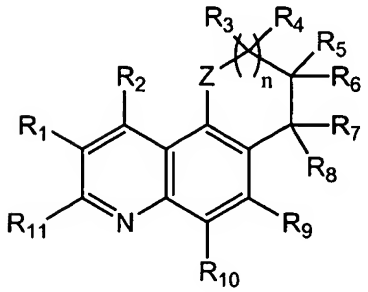

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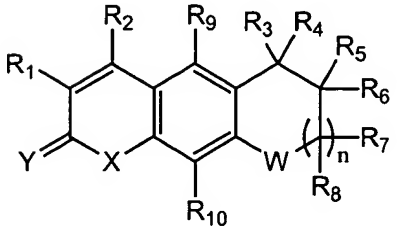

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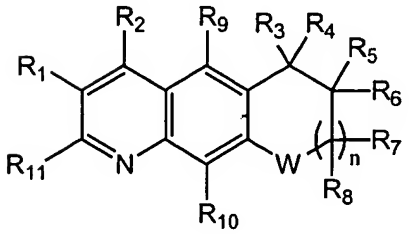

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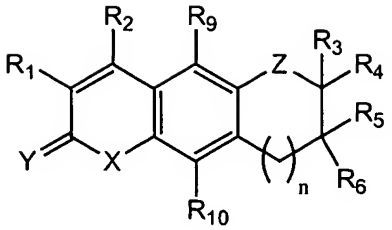

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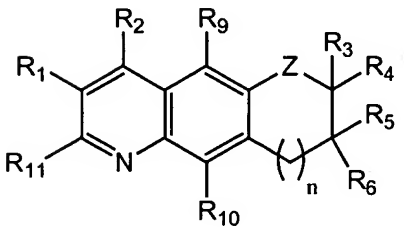


(VIII)

wherein:

R^1 is selected from the group of hydrogen, F, Cl, Br, I, NO_2, OR^{12}, SR^{12}, SOR^{12}, SO_2R^{12}, $NR^{12}R^{13}$, C_1-C_8 alkyl, C_1-C_8 haloalkyl and C_1-C_8 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted;

R^2 is selected from the group of hydrogen, F, Cl, Br, I, CH_3, CF_3, CHF_2, CH_2F, CF_2Cl, CN, CF_2OR^{12}, CH_2OR^{12}, OR^{12}, SR^{12}, SOR^{12}, SO_2R^{12}, $NR^{12}R^{13}$, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 heteroalkyl, C_2-C_8 alkenyl and C_2-C_8 alkynyl, wherein the alkyl, haloalkyl, heteroalkyl, alkenyl and alkynyl groups may be optionally substituted;

R^3 through R^8 each independently is selected from the group of hydrogen, F, Cl, Br, I, OR^{12}, $NR^{12}R^{13}$, SR^{12}, SOR^{12}, SO_2R^{12}, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 heteroalkyl, C_2-C_8 alkynyl, C_2-C_8 alkenyl, aryl, heteroaryl and arylalkyl, wherein the alkyl, haloalkyl, heteroalkyl, alkynyl, alkenyl, aryl, heteroaryl and arylalkyl groups may be optionally substituted; or

R^3 and R^5 taken together form a bond; or

R^5 and R^7 taken together form a bond; or

R^4 and R^6 taken together form a three- to eight-membered saturated or unsaturated carbocyclic or heterocyclic ring, wherein the carbocyclic or heterocyclic ring may optionally substituted; or

R^6 and R^8 taken together form a three- to eight-membered saturated or unsaturated carbocyclic or heterocyclic ring, wherein the carbocyclic or heterocyclic ring may optionally substituted;

R^9 and R^{10} each independently is selected from the group of hydrogen, F, Cl, Br, I, CN, OR^{12}, $NR^{12}R^{13}$, $C_m(R^{12})_{2m}OR^{13}$, SR^{12}, SOR^{12}, SO_2R^{12}, $NR^{12}C(O)R^{13}$, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 heteroalkyl and arylalkyl, wherein the alkyl, haloalkyl, heteroalkyl and arylalkyl groups may be optionally substituted;

R^{11} is selected from the group of hydrogen, F, Br, Cl, I, CN, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 heteroalkyl, OR^{14}, $NR^{14}R^{13}$, SR^{14}, CH_2R^{14}, $C(O)R^{14}$, CO_2R^{14}, $C(O)NR^{14}R^{13}$, SOR^{14} and SO_2R^{14}, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted;

R^{12} and R^{13} each independently is selected from the group of hydrogen, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 heteroalkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, heteroaryl and aryl, wherein the alkyl, haloalkyl, heteroalkyl, alkenyl, alkynyl, heteroaryl and aryl groups may be optionally substituted;

R^{14} is selected from the group of hydrogen, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 heteroalkyl, aryl, heteroaryl, $C(O)R^{15}$, CO_2R^{15} and $C(O)NR^{15}R^{16}$, wherein the alkyl, haloalkyl, heteroalkyl, aryl and heteroaryl groups may be optionally substituted;

R^{15} and R^{16} each independently is selected from the group of hydrogen, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted;

W is O or S;

X is selected from the group of O, S and $N\{R^{14}\}$;

Y is selected from the group of O, S, $N\{R^{12}\}$, $N\{OR^{12}\}$ and $CR^{12}R^{13}$;

Z is selected from the group of O, S and $N\{R^{12}\}$;

n is 0, 1 or 2;

m is 0, 1, or 2;

and pharmaceutically acceptable salts thereof.

In one aspect, the present the invention provides compounds represented by formula I through VIII. In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of an AR modulating compound of formula I through VIII shown above, wherein R^1 through R^{16}, m, n, W, X, Y, and Z are as described above.

In another aspect, the present invention provides a method of modulating processes mediated by ARs by administering to a patient a pharmaceutically effective amount of a compound of formula I through VIII shown above, wherein R^1 through R^{16}, m, n, W, X, Y, and Z are as described above. In one aspect, the modulation is activation, while in another aspect, the modulation is inhibition. In each case, the method involves administering to a patient a pharmaceutically effective amount of a compound of formula I through VIII shown above, wherein R^1 through R^{16}, m, n, W, X, Y, and Z are as described above.

With regard to the foregoing variables, the inventors contemplate any combination of the Markush groups as set forth above and as described in the following table.

Table A. Table of Markush Groups by Variable

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R^1	hydrogen, F, Cl, Br, I, C_1-C_6 alkyl, C_1-C_6 haloalkyl and C_1-C_6 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, F, Cl, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, F and optionally substituted C_1-C_2 alkyl	hydrogen and F
R^2	hydrogen, F, Cl, Br, CF_3, CF_2Cl, CF_2H, CFH_2, C_1-C_6 alkyl, C_1-C_6 haloalkyl and C_1-C_6 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted CF_2OR^{12}, CH_2OR^{12}, OR^{12}, SR^{12}, SOR^{12}, SO_2R^{12} and $NR^{12}R^{13}$	hydrogen, F, Cl, Br, CF_3, CF_2Cl, CF_2H, CFH_2, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 heteroalkyl, C_2-C_4 alkenyl and C_2-C_4 alkynyl, wherein the alkyl, haloalkyl, heteroalkyl, alkenyl and alkynyl groups may be optionally substituted	hydrogen, F, Cl, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, F, Cl, CF_3, CF_2Cl, CF_2H, CFH_2 and optionally substituted C_1-C_4 alkyl

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R^3	hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl and C_1-C_6 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen and optionally substituted C_1-C_4 alkyl	hydrogen
	R^3 and R^5 taken together form a bond			
R^4	hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl and C_1-C_6 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl and C_1-C_6 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen and C_1-C_4 alkyl
	R^4 and R^6 taken together form a four to six membered saturated or unsaturated carbocyclic or heterocyclic ring, wherein the carbocyclic or heterocyclic ring may be optionally substituted			

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R^5	hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl and C_1-C_6 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen and C_1-C_4 alkyl
	R^5 and R^7 taken together form a bond	R^5 and R^7 taken together form a bond		
	R^3 and R^5 taken together form a bond			

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R^6	hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 heteroalkyl, heteroaryl and aryl, wherein the alkyl, haloalkyl, heteroalkyl, heteroaryl and aryl groups may be optionally substituted	hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 heteroalkyl, heteroaryl and aryl, wherein the alkyl, haloalkyl, heteroalkyl, heteroaryl and aryl groups may be optionally substituted	hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl and C_1-C_6 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted
	R^4 and R^6 taken together form a four to six membered saturated or unsaturated carbocyclic or heterocyclic ring, wherein the carbocyclic or heterocyclic ring may be optionally substituted	R^6 and R^8 taken together form a four to six membered saturated or unsaturated carbocyclic or heterocyclic ring, wherein the carbocyclic or heterocyclic ring may optionally substituted	R^6 and R^8 taken together form a four to six membered saturated or unsaturated carbocyclic or heterocyclic ring, wherein the carbocyclic or heterocyclic ring may optionally substituted	
	R^6 and R^8 taken together form a three to eight membered saturated or unsaturated carbocyclic or heterocyclic ring, wherein the carbocyclic or heterocyclic ring may optionally substituted			

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R^7	hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl and C_1-C_6 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen and C_1-C_4 alkyl
	R^5 and R^7 taken together form a bond	R^5 and R^7 taken together form a bond		
R^8	hydrogen, C_1-C_6 alkyl, C_1-C_6 halo-alkyl, C_1-C_6 heteroalkyl, heteroaryl and aryl, wherein the alkyl, haloalkyl, heteroalkyl, heteroaryl and aryl groups may be optionally substituted	hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 heteroalkyl, heteroaryl and aryl, wherein the alkyl, haloalkyl, heteroalkyl, heteroaryl and aryl groups may be optionally substituted	hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl and C_1-C_6 heteroalkyl, wherein the alkyl, haloalkyl, heteroalkyl groups may be optionally substituted	hydrogen, methyl, and ethyl
	R^6 and R^8 taken together form a three- to eight-membered saturated or unsaturated carbocyclic or heterocyclic ring, wherein the carbocyclic or heterocyclic ring may be optionally substituted	R^6 and R^8 taken together form a four- to six-membered saturated or unsaturated carbocyclic or heterocyclic ring, wherein the carbocyclic or heterocyclic ring may optionally substituted	R^6 and R^8 taken together form a four- to six-membered saturated or unsaturated carbocyclic or heterocyclic ring, wherein the carbocyclic or heterocyclic ring may optionally substituted	R^6 and R^8 taken together form a four- to six-membered carbocyclic or heterocyclic ring, wherein the carbocyclic or heterocyclic ring may optionally substituted

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R^9	hydrogen, F, Cl, Br, C_1-C_6 alkyl, C_1-C_6 haloalkyl and C_1-C_6 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, F, Cl, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, F and CH_3	hydrogen
R^{10}	hydrogen, F, Cl, Br, C_1-C_6 alkyl, C_1-C_6 haloalkyl and C_1-C_6 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, F, Cl, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, F and CH_3	hydrogen
R^{11}	hydrogen, F, Br, Cl, CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 heteroalkyl, OR^{14}, $NR^{14}R^{13}$, SR^{14}, CH_2R^{14}, $C(O)R^{14}$, CO_2R^{14}, $C(O)NR^{14}R^{13}$, SOR^{14} and SO_2R^{14}, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, F, Cl, OR^{14}, SR^{14}, $NR^{14}R^{13}$, CH_2R^{14}, $C(O)R^{14}$, CO_2R^{14}, $C(O)NR^{14}R^{13}$, SOR^{14}, SO_2R^{14} and optionally substituted C_1-C_4 alkyl	hydrogen, F, Cl, OR^{14} and SR^{14}	OR^{14}

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R^{12}	hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 heteroalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, heteroaryl and aryl, wherein the alkyl, haloalkyl, heteroalkyl, alkenyl, alkynyl, heteroaryl and aryl groups may be optionally substituted	hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 heteroalkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl, wherein the alkyl, haloalkyl, heteroalkyl, alkenyl, and alkynyl groups may be optionally substituted	hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen and C_1-C_4 alkyl
R^{13}	hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 heteroalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, heteroaryl and aryl, wherein the alkyl, haloalkyl, heteroalkyl, alkenyl, alkynyl, heteroaryl and aryl groups may be optionally substituted	hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 heteroalkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl, wherein the alkyl, haloalkyl, heteroalkyl, alkenyl, and alkynyl groups may be optionally substituted	hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen and C_1-C_4 alkyl

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R^{14}	hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 heteroalkyl, aryl, heteroaryl, $C(O)R^{15}$, CO_2R^{15} and $C(O)NR^{15}R^{16}$, wherein the alkyl, haloalkyl, heteroalkyl, aryl and heteroaryl groups may be optionally substituted	hydrogen, $C(O)R^{15}$, $C(O)NR^{15}R^{16}$, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, optionally substituted C_1-C_2 alkyl, $C(O)CH_3$ and $C(O)N(CH_3)_2$	hydrogen and C_1-C_2 alkyl
R^{15}	hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_1-C_6 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, C_1-C_2 alkyl, C_1-C_2 haloalkyl, and C_1-C_2 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen and C_1-C_2 alkyl
R^{16}	hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl and C_1-C_6 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, C_1-C_2 alkyl, C_1-C_2 haloalkyl and C_1-C_2 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen and C_1-C_2 alkyl
W	O and S	O	S	
X	O and N{R^{14}}	N{R^{14}}	O	NH
Y	O and S	O	S	
Z	O and N{R^{12}}	N{R^{12}}	O	

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
n	0 and 1	0	1	
m	0 and 1	0	1	

The compounds of the present invention may be synthesized as pharmaceutically acceptable salts for incorporation into various pharmaceutical compositions. As used herein, pharmaceutically acceptable salts include, but are not limited to, hydrochloric, hydrobromic, hydroiodic, hydrofluoric, sulfuric, citric, maleic, acetic, lactic, nicotinic, succinic, oxalic, phosphoric, malonic, salicylic, phenylacetic, stearic, pyridine, ammonium, piperazine, diethylamine, nicotinamide, formic, urea, sodium, potassium, calcium, magnesium, zinc, lithium, cinnamic, methylamino, methanesulfonic, picric, tartaric, triethylamino, dimethylamino and tris(hydroxymethyl)aminomethane and the like and suitable combination of any two or more thereof. Additional pharmaceutically acceptable salts are known to those skilled in the art.

AR agonist, partial agonist and antagonist compounds of the present invention may be useful in the treatment of conditions including, but not limited to, hypogonadism, frailty, wasting diseases, cachexia, osteoporosis, hirsutism, acne, male-pattern baldness, prostatic hyperplasia, various hormone-dependent disorders and cancers, including, without limitation, prostate and breast cancer. The compounds of the present invention may also prove useful in male hormone replacement therapy, female androgen replacement therapy, stimulation of hematopoiesis, and as anabolic agents and libido stimulants.

It is understood by those skilled in the art that although the compounds of the present invention may be typically employed as selective agonists, partial agonists or antagonists, there may be instances where a compound with a mixed steroid receptor profile is desirable.

Furthermore, it is understood by those skilled in the art that the compounds of the present invention, as well as pharmaceutical compositions and formulations containing these compounds, can be used in a wide variety of combination therapies to treat the conditions and

diseases described above. Thus, the compounds of the present invention can be used in combination with other hormones and other therapies, including, without limitation, chemotherapeutic agents such as cytostatic and cytotoxic agents, immunological modifiers such as interferons, interleukins, growth hormones and other cytokines, hormone therapies, surgery and radiation therapy.

Representative AR modulator compounds (*i.e.*, agonists, partial agonists and antagonists) according to the present invention include:

5,6,7,8-Tetrahydro-7,7-dimethyl-4-trifluoromethylpyridino[3,2-*f*]quinolin-2(1*H*)-one (Compound **104**);

5,6,7,8-Tetrahydro-7,7-diethyl-4-trifluoromethylpyridino[3,2-*f*]quinolin-2(1*H*)-one (Compound **105**);

7,8-Dihydro-7,7-dimethyl-4-trifluoromethylpyridino[3,2-*f*]quinolin-2(1*H*)-one (Compound **106**);

5,6,7,8-Tetrahydro-7,7,8-trimethyl-4-trifluoromethylpyridino[3,2-*f*]quinolin-2(1*H*)-one (Compound **107**);

8-Ethyl-5,6,7,8-tetrahydro-7,7-dimethyl-4-trifluoromethylpyridino[3,2-*f*]quinolin-2(1*H*)-one (Compound **108**);

5,6,7,8-Tetrahydro-7,7-dimethyl-4-trifluoromethyl-8-propylpyridino[3,2-*f*]quinolin-2(1*H*)-one (Compound **109**);

8-(2,2,2-Trifluoroethyl)-5,6,7,8-tetrahydro-7,7-dimethyl-4-trifluoromethyl-pyridino[3,2-*f*]quinolin-2(1*H*)-one (Compound **110**);

6-Hydrazino-4-trifluoromethylquinolin-2(1*H*)-one (Compound **111**);

6-Methyl-4-trifluoromethyl-7H-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **112**);

5-Isopropyl-6-methyl-4-trifluoromethyl-7H-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **113**);

5-Allyl-6-methyl-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **114**);

5-(4-Methoxyphenyl)-6-methyl-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **115**);

5-(3-Trifluoromethylphenyl)-6-methyl-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **116**);

4-Trifluoromethyl-5,6,7,8-tetrahydrocyclopentano[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **117**);

4-Trifluoromethyl-5,6,7,8,9,10-hexahydrocycloheptano[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **118**);

(±)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-trifluoroethyl-4-trifluoromethylcyclopentano-[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **119**);

(±)-6,6a,7,8,9,9a(*cis*)-Hexahydro-6-trifluoroethyl-4-trifluoromethylcyclopentano-[i]pyrrolo[2,3-*g*]quinolin-2(1*H*)-one (Compound **120**);

(±)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-ethyl-4-trifluoromethylcyclopentano-[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **121**);

(±)-6,6a,7,8,9,9a(*cis*)-Hexahydro-6-ethyl-4-trifluoromethylcyclopentano-[i]pyrrolo[2,3-*g*]quinolin-2(1*H*)-one (Compound **122**);

(±)-5,6-Dihydro-5,6-*cis*-dimethyl-7-trifluoroethyl-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **123**);

(±)-7,8-Dihydro-7,8-*cis*-dimethyl-6-trifluoroethyl-4-trifluoromethyl-6*H*-pyrrolo[2,3-*g*]quinolin-2(1*H*)-one (Compound **124**);

(±)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-propyl-4-trifluoromethylcyclopentano-[g]pyrrolo-[3,2-*f*]quinolin-2(1*H*)-one (Compound **125**);

(±)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-(3-furanylmethyl)-4-trifluoromethyl-cyclopentano[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **126**);

(±)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-(3-thiophenemethyl)-4-trifluoromethyl-cyclopentano[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **127**);

(±)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-(2-methylpropyl)-4-trifluoromethyl-cyclopentano[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **128**);

(±)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-(2,2,2-chlorodifluoroethyl)-4-trifluoromethylcyclopentano[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **129**);

(±)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-cyclopropylmethyl-4-trifluoromethyl-cyclopentano[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **130**);

(±)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-(2,2-dimethoxyethyl)-4-trifluoromethyl-cyclopentano[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **131**);

(±)-4c,5,6,7,8,8a(*cis*)-Hexahydro-9-(2,2,2-trifluoroethyl)-4-trifluoromethyl-9H-cyclohexano[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **132**);

(±)-4c,5,6,7,8,9,9a(*cis*),10-Octahydro-10-(2,2,2-trifluoroethyl)-4-trifluoromethyl-cycloheptano[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **133**);

(±)-5,6- *cis*-Dihydro-6-ethyl-5-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **134**);

(±)-5,6- *cis*-Dihydro-5-butyl-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **135**);

(±)-5,6- *cis*-Dihydro-5-(4-nitrophenyl)-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **136**);

(±)-5,6- *cis*-Dihydro-5-(4-dimethylaminophenyl)-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **137**);

(±)-5,6- *cis*-Dihydro-5-(4-methoxyphenyl)-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **138**);

(±)-5,6- *cis*-Dihydro-5-(3-trifluoromethylphenyl)-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **139**);

(±)-5,6- *cis*-Dihydro-5-(4-fluorophenyl)-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **140**);

(±)-5,6-Dihydro-5-phenyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **141**);

(±)-5,6- *cis*-Dihydro-5-(4-methoxyphenyl)-6-methyl-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **142**);

(±)-5,6- *cis*-Dihydro-5-(4-methoxyphenyl)-6-methyl-7-(2,2-dimethoxyethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **143**);

(±)-5,6- *cis*-Dihydro-5-isopropyl-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **144**);

(±)-5,6-Dihydro-5-ethyl-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **145**);

(±)-5,6-Dihydro-5-ethyl-6-propyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **146**);

(±)-5,6-Dihydro-5-(2-ethoxycarbonylethyl)-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **147**);

6-Ethyl-5-methyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **148**);

(±)-5,6-*cis*-Dihydro-5-methyl-6-ethyl-7-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **149**);

5,6-Dimethyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **150**);

6-Ethyl-5-methyl-7-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **151**);

6-Methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **152**);

6-Ethyl-5-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **153**);

5-Ethyl-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **154**);

5-Ethyl-6-propyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **155**);

5,6,7,8-Tetrahydro-8-trifluoroethyl-4-trifluoromethylcyclopentano[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **156**);

8-Trifluoroethyl-4-trifluoromethyl-6,8-dihydrocyclopentano[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **157**);

9-Trifluoroethyl-4-trifluoromethyl-9*H*-benzo[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **158**);

6-Trifluoroethyl-4-trifluoromethyl-6,7,8,9-tetrahydrocyclopetano[*i*]pyrrolo[2,3-*g*]quinolin-2(1*H*)-one (Compound **159**);

5-(3-Trifluoromethylphenyl)-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **160**);

5-(4-Fluorophenyl)-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **161**);

5-(2-Ethoxycarbonylethyl)-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **162**);

7-Ethyl-8-methyl-6-(2,2,2-trifluoroethyl)-4-trifluoromethyl-6*H*-pyrrolo[2,3-*g*]quinolin-2(1*H*)-one (Compound **163**);

5-Hydroxymethyl-6-ethyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **164**);

5-Methyl-6-(1-hydroxyethyl)-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **165**);

5-Methyl-6-acetyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **166**);

5-Formyl-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **167**);

5-Acetyloxymethyl-6-ethyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **168**);

2-Acetyloxy-5-hydroxymethyl-6-ethyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinoline (Compound **169**);

6-Ethyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **170**);

5-Ethoxymethyl-6-ethyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **171**);

6-(1-Methoxyethyl)-5-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **172**);

7-Allyl-6-methyl-4-trifluoromethyl-5*H*-pyrrolo[2,3-*f*]quinolin-2(1*H*)-one (Compound **173**);

6-Ethyl-7-methyl-4-trifluoromethyl-5*H*-pyrrolo[2,3-*f*]quinolin-2(1*H*)-one (Compound **175**);

7-(3-Trifluoromethylphenyl)-6-methyl-4-trifluoromethyl-5*H*-pyrrolo[2,3-*f*]quinolin-2(1*H*)-one (Compound **176**);

7-(2-Hydroxyethyl)-6-methyl-4-trifluoromethyl-5*H*-pyrrolo[2,3-*f*]quinolin-2(1*H*)-one (Compound **177**);

(+)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-trifluoroethyl-4-trifluoromethylcyclopentano-[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **178**);

(−)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-trifluoroethyl-4-trifluoromethylcyclopentano-[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **179**);

4-Trifluoromethyl-6,7-dihydro-7,7,9-trimethyl-pyrido[2,3-*g*]quinolin-2(1*H*)-one (Compound **180**);

8-(2,2,2-Trifluoroethyl)-5,6,7,8-tetrahydro-5,7,7-trimethylpyrido[3,2-*f*]quinolin-2(1*H*)-one (Compound **182**);

4,5,7-Tri(trifluoromethyl)pyrido[3,2-*f*]quinolin-2(1*H*)-one (Compound **185**);

5,7-Bis(trifluoromethyl)pyrido[3,2-*f*]quinolin-2(1*H*)-one (Compound **186**);

4-Trifluoromethyl-7-methyl-6,7,8,9-tetrahydropyrido[2,3-*g*]quinolin-2(1*H*)-one (Compound **187**);

4-Trifluoromethyl-7,8-dihydro-6*H*-pyrrolo[2,3-*g*]quinolin-2(1*H*)-one (Compound **190**);

4-Trifluoromethyl-5,6,7,8-tetrahydropyrido[2,3-*g*]quinolin-2(1*H*)-one (Compound **192**);

4-Trifluoromethyl-7-methyl-6-propyl-6,7,8,9-tetrahydropyrido[2,3-*g*]quinolin-2(1*H*)-one (Compound **194**);

4-Trifluoromethyl-7-methyl-6-cyclopropylmethyl-6,7,8,9-tetrahydropyrido[2,3-*g*]quinolin-2(1*H*)-one (Compound **195**);

4-Trifluoromethyl-7-methyl-6-ethyl-6,7,8,9-tetrahydropyrido[2,3-*g*]quinolin-2(1*H*)-one (Compound **196**);

4-Trifluoromethyl-7-methyl-6-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydropyrido[2,3-*g*]quinolin-2(1*H*)-one (Compound **197**);

4-Trifluoromethyl-6-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydropyrido[2,3-*g*]quinolin-2(1*H*)-one (Compound **198**);

4-Trifluoromethyl-6-propyl-6,7,8,9-tetrahydropyrido[2,3-*g*]quinolin-2(1*H*)-one (Compound **199**);

4-Trifluoromethyl-6-ethyl-6,7,8,9-tetrahydropyrido[2,3-*g*]quinolin-2(1*H*)-one (Compound **200**);

4-Trifluoromethyl-6-cyclopropylmethyl-6,7,8,9-tetrahydropyrido[2,3-*g*]quinolin-2(1*H*)-one (Compound **201**);

6,7-Dihydro-8,8-dimethyl-4-(trifluoromethyl)-8*H*-pyrano[3,2-*g*]quinolin-2(1*H*)-one (Compound **202**);

6,7-Dihydro-8,8,10-trimethyl-4-(trifluoromethyl)-8*H*-pyrano[3,2-*g*]quinolin-2(1*H*)-one (Compound **206**);

(±)-6,7-Dihydro-6-ethyl-4-methyl-8*H*-pyrano[3,2-*g*]quinolin-2(1*H*)-one (Compound **210**);

(±)-7,8-Dihydro-8-ethyl-4-methyl-6*H*-pyrano[2,3-*f*]quinolin-2(1*H*)-one (Compound **215**);

(±)-6,7-Dihydro-6-ethyl-4-trifluoromethyl-8*H*-pyrano[3,2-*g*]quinolin-2(1*H*)-one (Compound **216**);

(-)-6,7-Dihydro-6-ethyl-4-trifluoromethyl-8*H*-pyrano[3,2-*g*]quinolin-2(1*H*)-one (Compound **217**);

(+)-6,7-Dihydro-6-ethyl-4-trifluoromethyl-8*H*-pyrano[3,2-*g*]quinolin-2(1*H*)-one (Compound **218**);

(±)-6,7-Dihydro-6-ethyl-3-fluoro-4-trifluoromethyl-8*H*-pyrano[3,2-*g*]quinolin-2(1*H*)-one (Compound **219**);

(±)-6,7-Dihydro-6-ethyl-4-trifluoromethyl-1-methyl-8*H*-pyrano[3,2-*g*]quinolin-2(1*H*)-one (Compound **220**);

(±)-6,7-Dihydro-6-ethyl-3-fluoro-4-trifluoromethyl-1-methyl-8*H*-pyrano[3,2-*g*]quinolin-2(1*H*)-one (Compound **221**);

(±)-6,7-Dihydro-6-ethyl-2,4-bis(trifluoromethyl)-8*H*-pyrano[3,2-*g*]quinoline (Compound **222**);

6,8,8-Trimethyl-4-trifluoromethyl-8*H*-pyrano[3,2-*g*]coumarin (Compound **223**);

6-Ethyl-8,8-dimethyl-4-trifluoromethyl-8*H*-pyrano[3,2-*g*]coumarin (Compound **227**);

(±)-5,6-Dihydro-6-hydroxymethyl-4-trifluoromethylpyrrolo[3,2-f]quinolin-2(1H)-one (Compound **228**);

(±)-5,6-Dihydro-7-ethyl-6-hydroxymethyl-4-trifluoromethylpyrrolo[3,2-f]quinolin-2(1H)-one (Compound **229**);

7,8-Dihydro-6-(2,2,2-trifluoroethyl)-4-trifluoromethylpyrrolo[2,3-g]quinolin-2(1H)-one (Compound **230**);

6-(2,2,2-Trifluoroethyl)-4-trifluoromethylpyrrolo[2,3-g]quinolin-2(1H)-one (Compound **231**);

8-Chloro-6-(2,2,2-trifluoroethyl)-4-trifluoromethylpyrrolo[2,3-g]quinolin-2(1H)-one (Compound **232**);

5-Methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethylpyrrolo[3,2-f]quinolin-2(1H)-one (Compound **233**);

6-Formyl-5-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7H-pyrrolo[3,2-f]quinolin-2(1H)-one (Compound **234**);

5,6-Dimethyl-7-(2,2-difluorovinyl)-4-trifluoromethyl-7H-pyrrolo[3,2-f]quinolin-2(1H)-one (Compound **235**).

Within such group, representative compounds include:

8-Ethyl-5,6,7,8-tetrahydro-7,7-dimethyl-4-trifluoromethylpyridino[3,2-*f*]quinolin-2(1*H*)-one (Compound **108**);

5,6,7,8-Tetrahydro-7,7-dimethyl-4-trifluoromethyl-8-propylpyridino[3,2-*f*]quinolin-2(1*H*)-one (Compound **109**);

8-(2,2,2-Trifluoroethyl)-5,6,7,8-tetrahydro-7,7-dimethyl-4-trifluoromethyl-pyridino[3,2-*f*]quinolin-2(1*H*)-one (Compound **110**);

(±)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-trifluoroethyl-4-trifluoromethylcyclopentano-[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **119**);

(±)-6,6a,7,8,9,9a(*cis*)-Hexahydro-6-trifluoroethyl-4-trifluoromethylcyclopentano-[i]pyrrolo[2,3-*g*]quinolin-2(1*H*)-one (Compound **120**);

(±)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-ethyl-4-trifluoromethylcyclopentano-[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **121**);

(±)-5,6-Dihydro-5,6-*cis*-dimethyl-7-trifluoroethyl-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **123**);

(±)-7,8-Dihydro-7,8-*cis*-dimethyl-6-trifluoroethyl-4-trifluoromethyl-6*H*-pyrrolo[2,3-*g*]quinolin-2(1*H*)-one (Compound **124**);

(±)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-propyl-4-trifluoromethylcyclopentano-[g]pyrrolo-[3,2-*f*]quinolin-2(1*H*)-one (Compound **125**);

(±)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-(2,2,2-chlorodifluoroethyl)-4-trifluoromethylcyclopentano[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **129**);

(±)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-cyclopropylmethyl-4-trifluoromethyl-cyclopentano[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **130**);

(±)-4c,5,6,7,8,8a(*cis*)-Hexahydro-9-(2,2,2-trifluoroethyl)-4-trifluoromethyl-9H-cyclohexano[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **132**);

(±)-5,6- *cis*-Dihydro-6-ethyl-5-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **134**);

(±)-5,6- *cis*-Dihydro-5-butyl-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **135**);

(±)-5,6-Dihydro-5-ethyl-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **145**);

(±)-5,6-Dihydro-5-ethyl-6-propyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **146**);

(±)-5,6-*cis*-Dihydro-5-methyl-6-ethyl-7-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **149**);

5,6-Dimethyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **150**);

6-Methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **152**);

6-Ethyl-5-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **153**);

5-Ethyl-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **154**);

5,6,7,8-Tetrahydro-8-trifluoroethyl-4-trifluoromethylcyclopentano[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **156**);

6-Trifluoroethyl-4-trifluoromethyl-6,7,8,9-tetrahydrocyclopetano[*i*]pyrrolo[2,3-*g*]quinolin-2(1*H*)-one (Compound **159**);

7-Ethyl-8-methyl-6-(2,2,2-trifluoroethyl)-4-trifluoromethyl-6*H*-pyrrolo[2,3-*g*]quinolin-2(1*H*)-one (Compound **163**);

6-Ethyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **170**);

(+)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-trifluoroethyl-4-trifluoromethylcyclopentano-[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **178**);

(−)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-trifluoroethyl-4-trifluoromethylcyclopentano-[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **179**);

8-(2,2,2-Trifluoroethyl)-5,6,7,8-tetrahydro-5,7,7-trimethylpyrido[3,2-*f*]quinolin-2(1*H*)-one (Compound **182**);

4-Trifluoromethyl-7-methyl-6-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydropyrido[2,3-*g*]quinolin-2(1*H*)-one (Compound **197**);

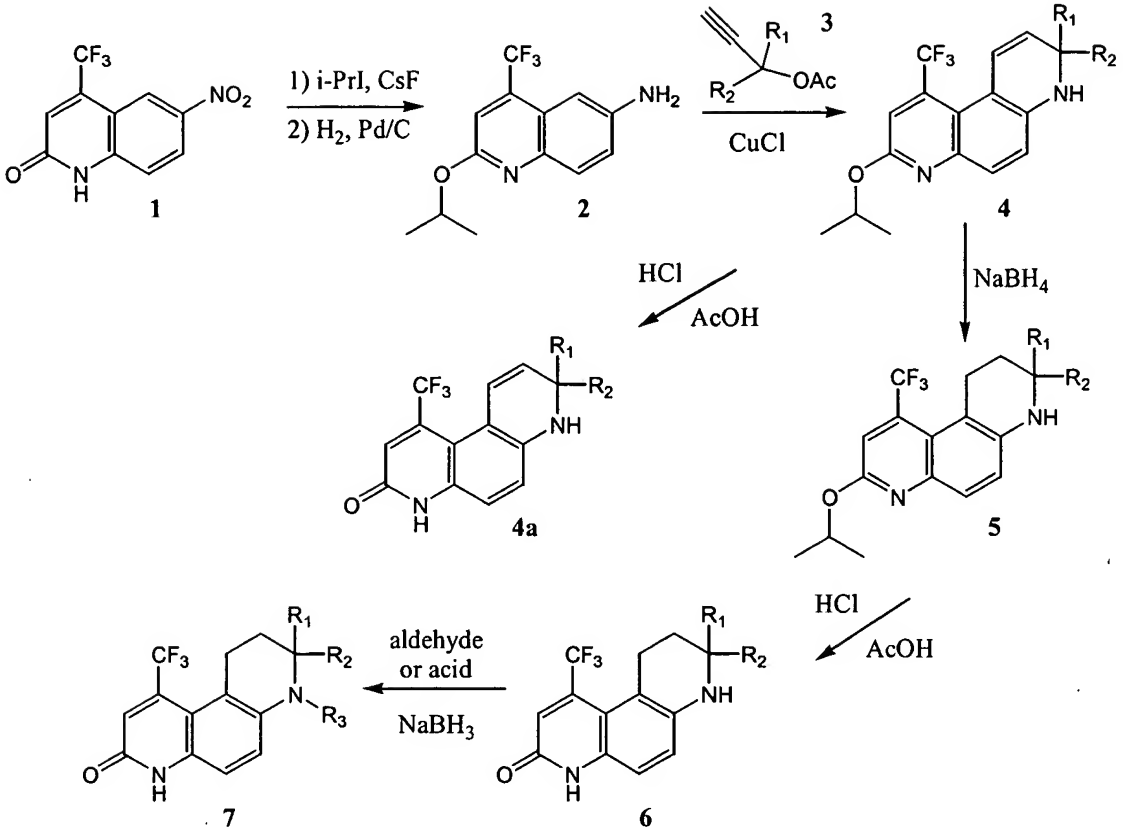
6,7-Dihydro-8,8-dimethyl-4-(trifluoromethyl)-8*H*-pyrano[3,2-*g*]quinolin-2(1*H*)-one (Compound **202**);

(-)-6,7-Dihydro-6-ethyl-4-trifluoromethyl-8*H*-pyrano[3,2-*g*]quinolin-2(1*H*)-one (Compound **217**); and

(+)-6,7-Dihydro-6-ethyl-4-trifluoromethyl-8*H*-pyrano[3,2-*g*]quinolin-2(1*H*)-one (Compound **218**).

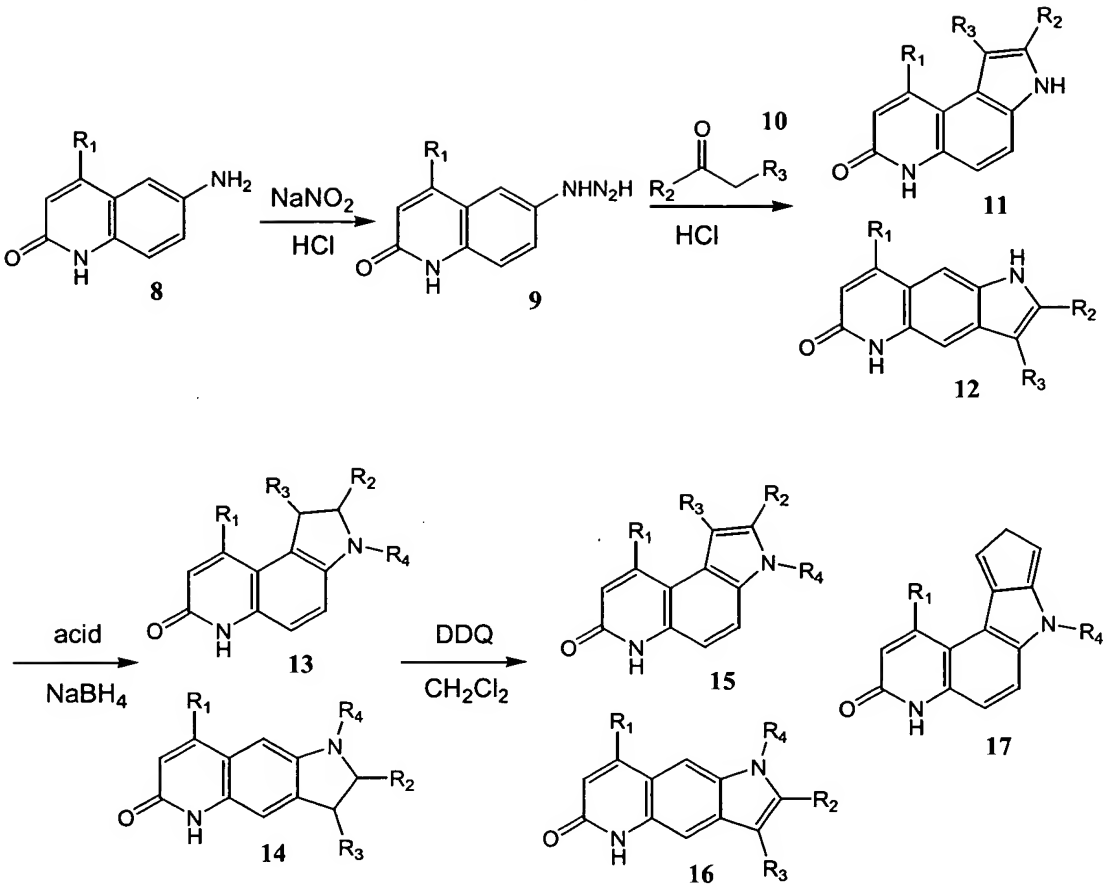
The sequences of steps for several general schemes to synthesize the compounds of the present invention are shown below. In each of the Schemes the R groups (*e.g.*, R_1, R_2, etc.) correspond to the specific substitution patterns noted in the Examples. However, it will be understood by those skilled in the art that other functionalities disclosed herein at the indicated positions of compounds of formulas I through VIII are also potential substituents for the analogous positions on the structures within the Schemes.

Scheme I



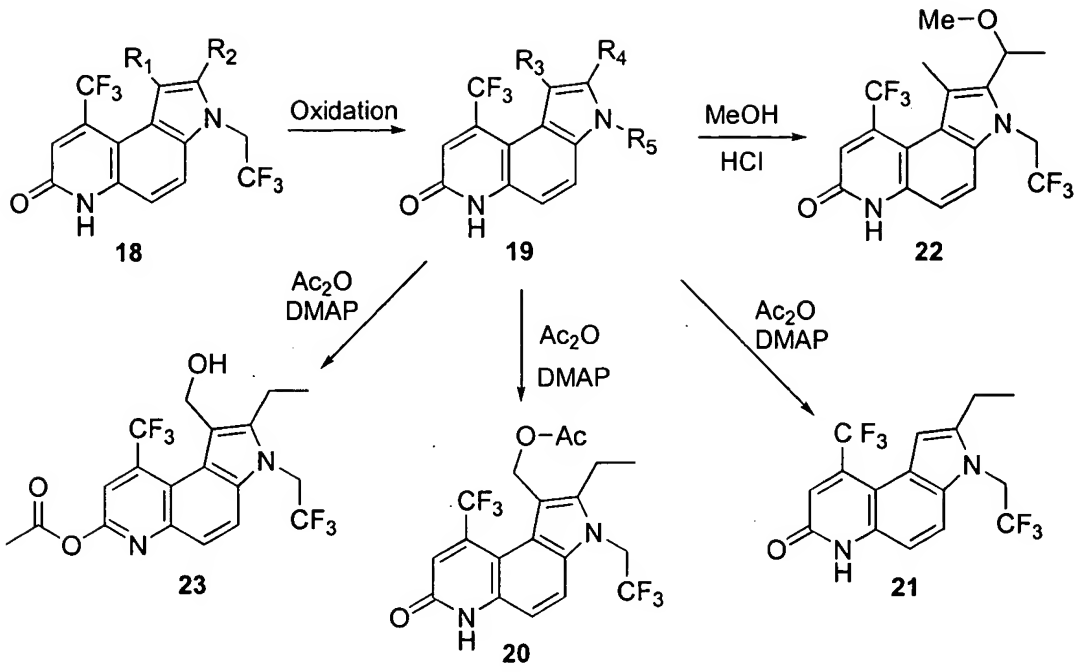
Scheme **I** describes the synthesis of the tricyclic quinolinones of structure **7**. Treatment of 6-nitro-2-quinolinone (structure **1**) with alkyl halide such as 2-iodopropane in the presence of CsF followed by a palladium catalyzed hydrogenation provide aminoquinoline of structure **2**. Copper catalyzed coupling reaction of structure **2** and propargyl acetate such as structure **3** followed by a copper catalyzed cyclization regioselectively afford tricyclic quinoline derivatives of structure **4**. Reduction of dihydroquinolines of structure **4** with $NaBH_4$ gives tetrahydroquinolines of structure **5**. Acid catalyzed hydrolysis of structure **5** provides quinolinones of structure **6**. Selective alkylation at 8-position with an aldehyde or acid in the presence of a reducing agent such as $NaBH_4$ afford compounds of structure **7**.

Scheme II



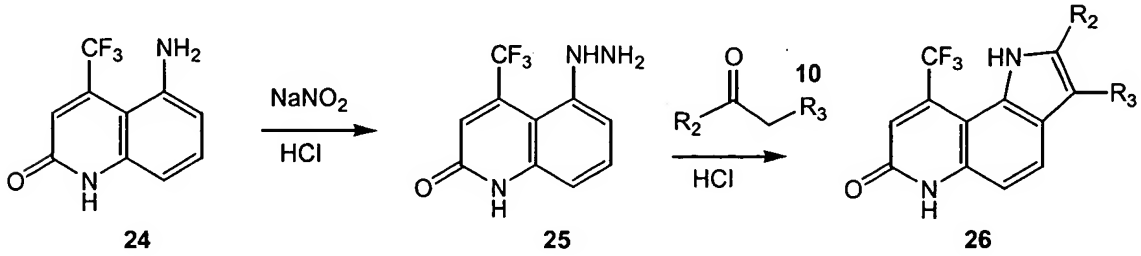
Scheme **II** describes the synthesis of angular and linear indole/indoline analogues of structures **13-17**. Treatment of 6-amino-2-quinolinones of structure **8** with $NaNO_2$ in strongly acidic conditions such as concentrated HCl generates hydrozines of structure **9**. Reaction of compound of structure **9** with a ketone such as structure **10** in acidic conditions affords a mixture of pyrroloquinolinones of structures **11** and **12**, which can be separated by chromatography. Reductive alkylation of the indole nitrogen atom in structure **11** or **12** with an acid or aldehyde in the presence of a reducing agent such as $NaBH_4$ results in the formation of the reduced and alkylated products of structure **13** or **14**. Oxidation of structure **13** or **14** provides analogues of structure **15, 16** or **17**.

Scheme III



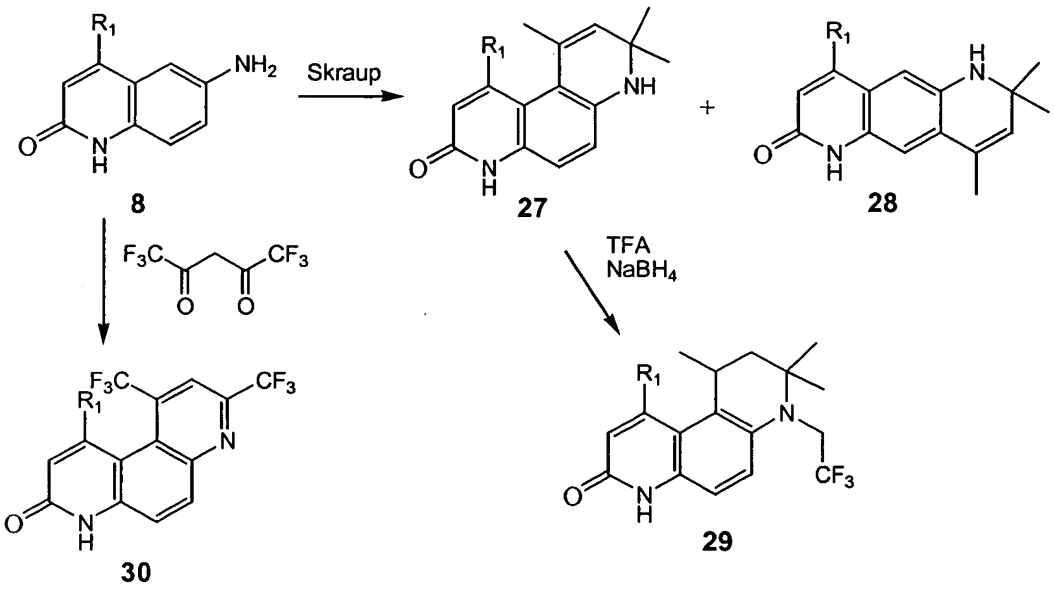
Scheme **III** describes side chain manipulation of compounds of structure **18**. Treatment of compounds of structure **18** with an oxidating reagent such as DDQ or MnO_2 affords products of structure **19**. Acylation of compounds of structure **19** with acetyl anhydride in the presence of DMAP generates compounds of structures **20** and **23**. Compounds of structure **21** is a by-product of the acylation reaction. Treatment of compounds of structure **19** with HCl in methanol gives the ether products of structure **22**.

Scheme IV



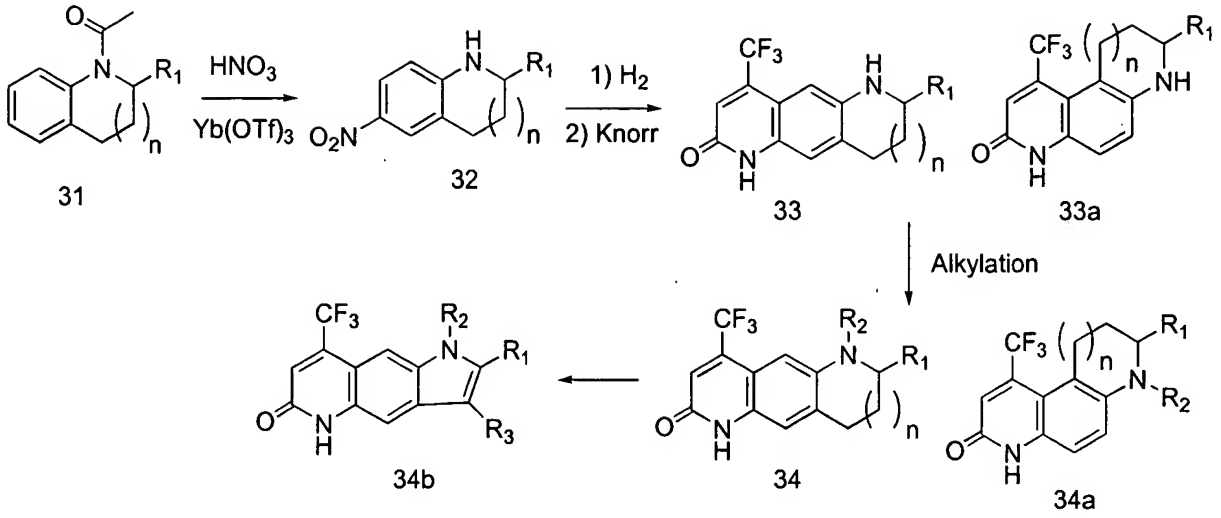
Scheme **IV** describes the preparation of tricyclic compounds of structure **26** by Fischer indole synthesis. Treatment of the 5-aminoquinolinone of structure **24** with $NaNO_2$ in acidic conditions provides the hydrozine intermediates of structure **25**. Condensation of the hydrozine (structure **25**) and a ketone of structure **10** followed by acid catalyzed cyclization afford compounds of structure **26**.

Scheme V



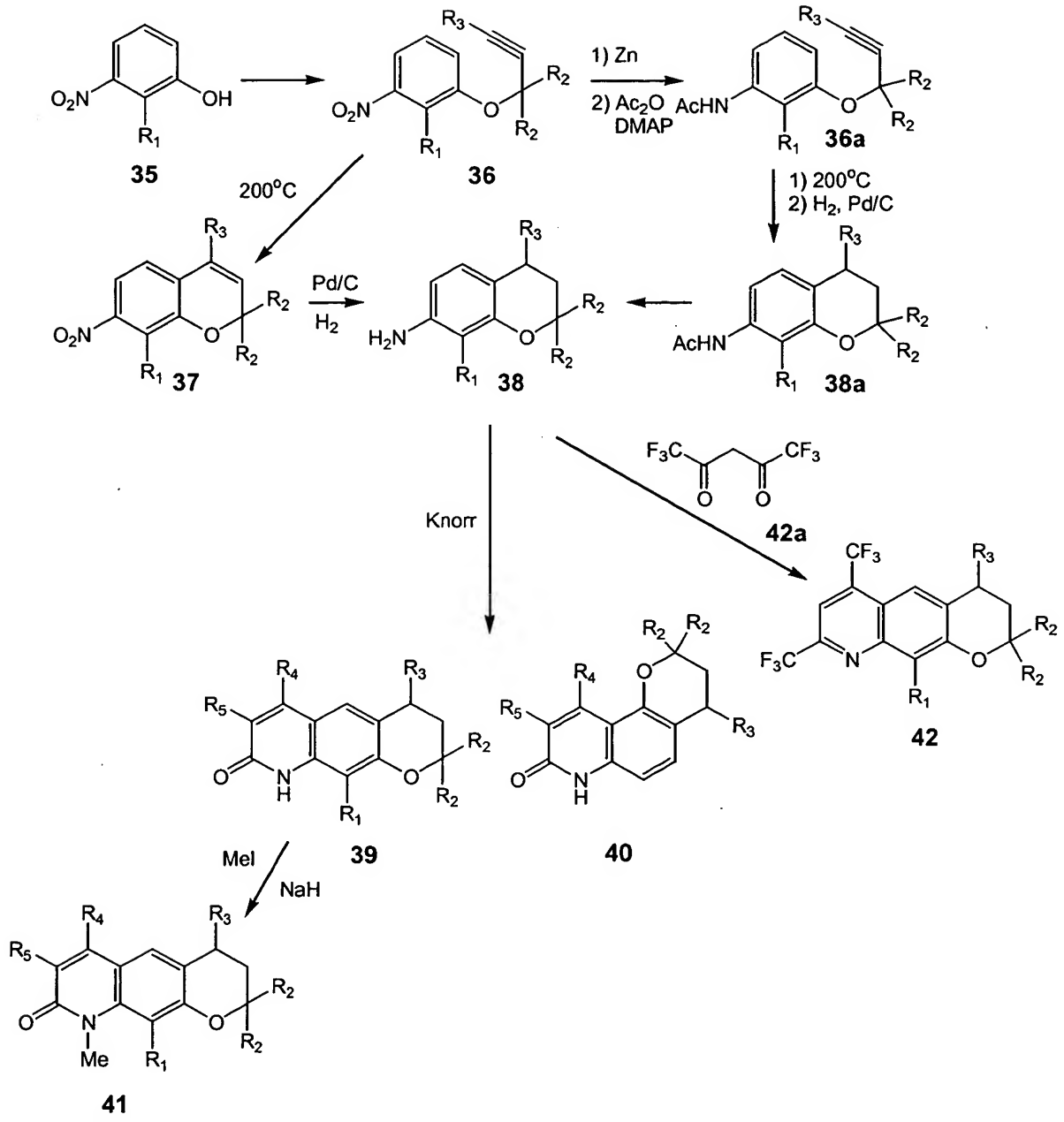
Scheme **V** describes the preparation of tricyclic analogues from 6-aminoquinolinones of structure **8**. Skraup reaction of an aminoquinoline of structure **8** in acetone at high temperature affords compounds of structures **27** or **28** that depends on the substituent R_1. Treatment of compounds of structure **27** under a reductive alkylation condition such as $NaBH_4$ in TFA provides compounds of structure **29**. Condensation of the aminoquinolines of structure **8** with 1,1,1,5,5,5-hexafluoro-2,4-pentadione affords compounds of structure **30**.

Scheme VI



Scheme **VI** describes the synthesis of the tricyclic compounds of structures **34** and **34a**. Nitration of a tetrahydroquinoline of structure **31** provides compounds of structure **32**. Palladium catalyzed hydrogenation of compounds of structure **32** followed by the Knorr reaction afford the mixture compounds of structures **33** and **33a**. Selective alkylation of compounds of structures **33** and **33a** gives compounds of structures **34** and **34a**.

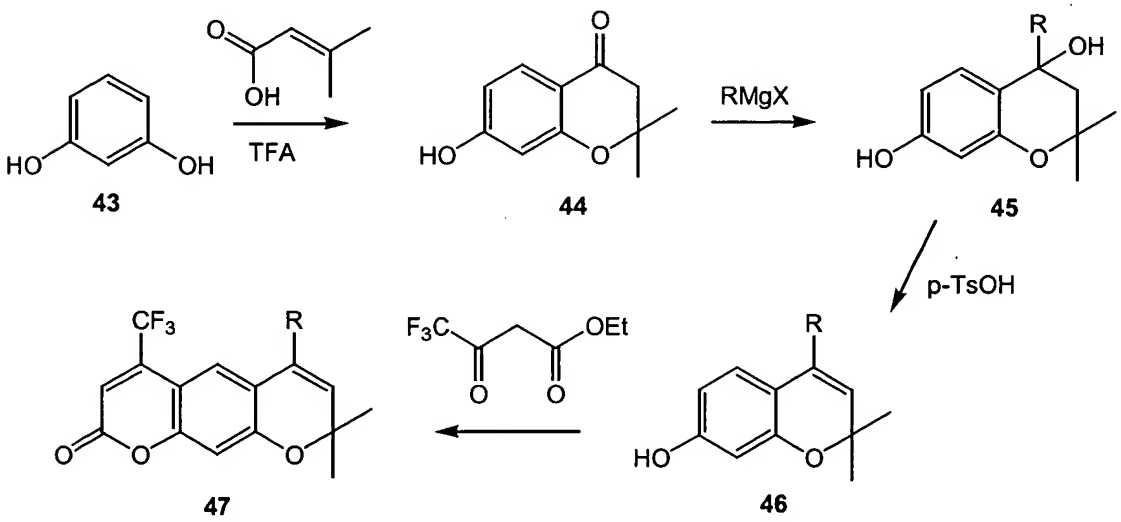
Scheme VII



Scheme **VII** describes the synthesis of the tricyclic pyranoquinolines of structures **39** and **41**. Alkylation of 3-nitrophenols of structure **35** gives compounds of structure **36**. Thermal cyclization of the propargyl ethers of structure **36** affords the chromenes of structure **37**. Reduction of the nitro group by hydrogenation provides the aminochromans of structure

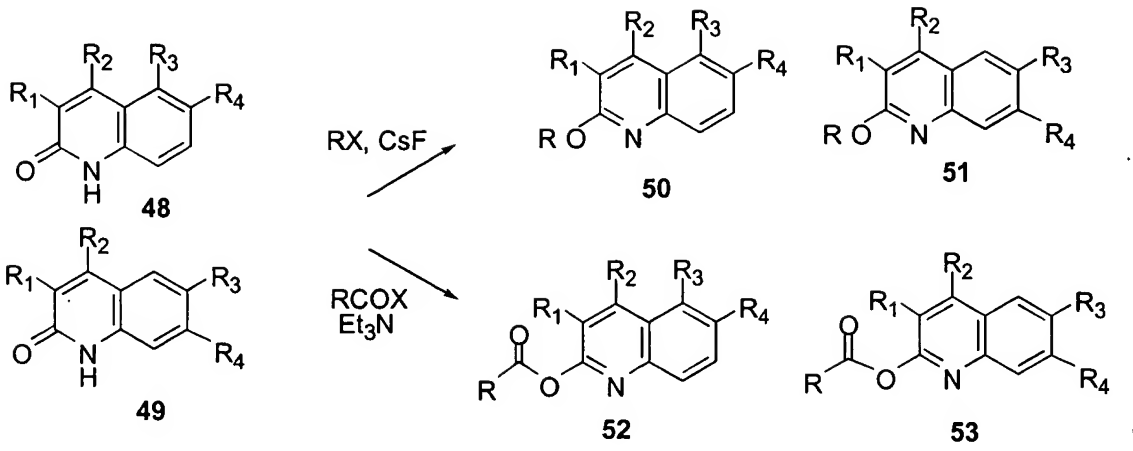
38. An alternate route starts with reduction of the nitro group in compounds of structure **36** with zinc powder followed by acylation to give the compound of structure **36a**. Cyclization at high temperature, followed by palladium catalyzed hydrogenation, provides the chroman of structure **38a**. Hydrolysis of the acetyl group affords aminochroman of structure **38**. Treatment of compounds of structure **38** with a ketoester such as ethyl 4,4,4-trifluoro-3-ketobutyrate under Knorr condition gives compounds of structures **39** and **40**. In the case when the diketone of structure **42a** is used, a quinoline of structure **42** is the product. Methylation of compounds of structure **39** with iodomethane and sodium hydride affords compounds of structure **41**.

Scheme VIII



Scheme **VIII** describes the synthesis of the tricyclic coumarins of structure **47**. Annulation to form compounds of structure **44** is accomplished by heating 1,3-resorcinol and 3,3-dimethylacrylic acid in TFA. Grignard addition to chromenones of structure **44** affords compounds of structure **45**, which is dehydrated under acidic condition to give chromenes of structure **46**. Treatment of the hydroxychromenes of structure **46** with a ketoester such as ethyl 4,4,4-trifluoroacetoacetate in the presence of $POCl_3$ affords compounds of structure **47**.

Scheme IX



Scheme **IX** describes the general procedure to convert the 2-quinolinone derivatives to the typical 2-substituted quinoline derivatives. Treatment of compounds of structures **48** and **49** with a haloalkyl in the presence of a catalyst such as CsF produces the corresponding 2-alkoxy quinoline compounds of structures **50** and **51**. Treatment of compounds of structures **48** and **49** with an acyl halide in the presence of a base, such as triethylamine, affords the 2-acyloxy quinolines of structures **52** and **53**.

The compounds of the present invention also include racemates, stereoisomers, optically pure enantiomers and mixtures of said compounds, including isotopically-labeled and radio-labeled compounds. Such isomers can be isolated by standard resolution techniques, including fractional crystallization and chiral column chromatography.

As noted above, the androgen receptor modulator compounds of the present invention can be combined in a mixture with a pharmaceutically acceptable carrier to provide pharmaceutical compositions useful for treating the biological conditions or disorders noted herein in mammalian and particularly in human patients. The particular carrier employed in these pharmaceutical compositions may take a wide variety of forms depending upon the type of administration desired. Suitable administration routes include enteral (*e.g.*, oral), topical, suppository and parenteral (*e.g.*, intravenous, intramuscular and subcutaneous).

In preparing the compositions in oral liquid dosage forms (*e.g.*, suspensions, elixirs and solutions), typical pharmaceutical media, such as water, glycols, oils, alcohols, flavoring

agents, preservatives, coloring agents and the like can be employed. Similarly, when preparing oral solid dosage forms (*e.g.*, powders, tablets and capsules), carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like may be employed. Due to their ease of administration, tablets and capsules represent a desirable oral dosage form for the pharmaceutical compositions of the present invention.

For parenteral administration, the carrier typically will include sterile water, although other ingredients that aid in solubility or serve as preservatives, may also be included. Furthermore, injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed.

For topical administration, the compounds of the present invention may be formulated using bland, moisturizing bases, such as ointments or creams. Examples of suitable ointment bases are petrolatum, petrolatum plus volatile silicones, lanolin and water in oil emulsions such as Eucerin™, available from Beiersdorf (Cincinnati, Ohio). Examples of suitable cream bases are Nivea™ Cream, available from Beiersdorf (Cincinnati, Ohio), cold cream (USP), Purpose Cream™, available from Johnson & Johnson (New Brunswick, New Jersey), hydrophilic ointment (USP) and Lubriderm™, available from Warner-Lambert (Morris Plains, New Jersey).

The pharmaceutical compositions and compounds of the present invention generally will be administered in the form of a dosage unit (*e.g.*, tablet, capsule, etc.). The compounds of the present invention generally are administered in a daily dosage of from about 1 μg/kg of body weight to about 500 mg/kg of body weight. Typically, the compounds of the present invention are administered in a daily dosage of from about 10 μg/kg to about 250 mg/kg of body weight. Most often, the compounds of the present invention are administered in a daily dosage of from about 20 μg/kg to about 100 mg/kg body weight. As recognized by those skilled in the art, the particular quantity of pharmaceutical composition according to the present invention administered to a patient will depend upon a number of factors, including, without limitation, the biological activity desired, the condition of the patient and the patient's tolerance for the drug.

The compounds of this invention also have utility when labeled (*e.g.*, radio-labeled, isotopically-labeled and the like) as ligands for use in assays to determine the presence of AR in a cell background or extract. They are particularly useful due to their ability to selectively activate androgen receptors and can therefore be used to determine the presence of such receptors in the presence of other steroid receptors or related intracellular receptors.

These invention methods comprise contacting the cell or cell extract with the compounds of the present invention which have been labeled and testing the contacted cell or cell extract to determine the presence of AR. Testing can be accomplished *via* testing for activation of androgen receptor(s) (*e.g.*, *via* elevated presence of the product of androgen mediated process(es)), *via* separation of the bound compound/receptor combination and the like, which techniques are known to those of skill in the art.

Due to the selective specificity of the compounds of this invention for steroid receptors, these compounds can be used to purify samples of steroid receptors *in vitro*. Such purification can be carried out by mixing samples containing steroid receptors with one or more of the compounds of the present invention so that the compounds bind to the receptors of choice and then isolating the bound ligand/receptor combination by separation techniques which are known to those of skill in the art. These techniques include column separation, filtration, centrifugation, tagging and physical separation and antibody complexing, among others.

The compounds and pharmaceutical compositions of the present invention can be used in the treatment of the diseases and conditions described herein. In this regard, the compounds and compositions of the present invention may prove particularly useful as modulators of male sex steroid-dependent diseases and conditions such as the treatment of hypogonadism, sexual dysfunction, acne, male-pattern baldness, wasting diseases, hirsutism, prostatic hyperplasia, osteoporosis, impotence, cancer cachexia, various hormone-dependent cancers, including, without limitation, prostate and breast cancer. The compounds of the present invention may also prove useful in male hormone replacement therapy, stimulation of hematopoiesis, male contraception and as anabolic agents.

The compounds of the present invention may be extremely potent activators of AR, displaying 50% maximal activation of AR (*e.g.*, activation of AR, determined by measurement of luciferase production levels compared to levels achieved by dihydrotestosterone (DHT)) at a concentration of less than 100 nM (Cotransfection assay concentration), at a concentration of less than 50 nM, at a concentration of less than 20 nM, or even at a concentration of 10 nM or less. (See, for example, Biological Examples.)

Alternatively, the compounds of the present invention may be extremely potent inhibitors of AR, displaying 50% maximal inhibition of AR (e.g., inhibition of AR, determined by measurement of luciferase production levels compared to levels achieved by dihydrotestosterone (DHT)) at a concentration of less than 100 nM (Cotransfection assay concentration), at a concentration of less than 50 nM, at a concentration of less than 20 nM, or even at a concentration of 10 nM or less. (See, for example, Biological Examples.)

In one embodiment, the selective compounds of the present invention generally do not display undesired cross-reactivity with other steroid receptors, as is seen with the compound mifepristone (RU486; Roussel Uclaf), a known PR antagonist that displays an undesirable cross reactivity on GR and AR, thereby limiting its use in long-term, chronic administration.

The invention will be further illustrated by reference to the following non - limiting Examples.

EXAMPLE 1

7,8-Dihydro-7,7-dimethyl-2-isopropoxy-4-trifluoromethyl-8H-pyridino[3,2-*f*]quinoline (Compound **101**, Structure **4** of Scheme I, where $R_1 = R_2$ = methyl)

6-Amino-2-isopropoxy-4-trifluoromethylquinoline (Compound **102**, Structure **2** of Scheme I):

In a 250-mL r.b. flask, a solution of 4-trifluoromethyl-6-nitroquinolinone (structure **1** of Scheme I) (3.78 g, 14.6 mmol) in DMF (75 mL) was treated with CsF (12.41 g, 73 mmol, 5.0 equiv.) and 2-iodopropane (11.09 g, 73 mmol, 5.0 equiv). The reaction mixture was stirred at room temperature (rt) for 18 h. The reaction mixture was quenched with H_2O (100 mL) and

extracted with EtOAc (3 x 200 mL). The combined EtOAc extracts were washed with saturated aqueous NH_4Cl solution (300 mL), H_2O (300 mL) and brine (300 mL). Dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 5 x 20 cm, 2% EtOAc in hexane as eluent) to afford 3.94 g (90%) of the 2-isopropoxyquinoline as a white solid. R_f 0.81 (SiO_2, 10% EtOAc-hexane). ^1H NMR (400 MHz, $CDCl_3$) 8.93 (s, 1H), 8.47 (dd, 1H, J = 9.2, 2.5) 7.98 (d, 1H, J = 9.2), 7.32 (s, 1H), 5.62 (septet, 1H, J = 6.2), 1.45 (d, 1H, J = 6.2).

In a 100-mL r.b. flask, a solution of 2-isopropoxy-4-trifluoromethyl-6-nitroquinolinone (1.0 g, 3.3 mmol) in a 3:1 ratio of CH_2Cl_2/MeOH (40 mL) was treated with 10% Pd/C (168 mg, 16 wt. % equiv). The resulting mixture was stirred under H_2 (1 atm) at rt for 18 h. The reaction mixture was filtered through a pad of celite and the celite cake was rinsed with MeOH (100 mL). The filtrate was concentrated *in vacuo* to give 0.85 g (95%) of compound **102** as colorless oil that was used immediately in the next reaction without further purification. R_f 0.27 (SiO_2, 10% EtOAc-hexane). ^1H NMR (400 MHz, $CDCl_3$) 7.70 (d, 1H, J = 9.6) 7.13 (m, 3H), 5.49 (septet, 1H, J = 6.2), 3.89 (s, 2H), 1.39 (d, 1H, J = 6.2).

7,8-Dihydro-7,7-dimethyl-2-isopropoxy-4-trifluoromethyl-8H-pyridino[3,2-*f*]quinoline (Compound **101**, Structure **4** of Scheme I, where $R_1 = R_2$ = methyl):

In a 250-mL r.b. flask, a solution of compound **102** (4.55g, 16.8 mmol) in THF (150 mL) was treated with Cu(I)Cl (0.167g, 0.168 mmol, 10 mol%) and 2-acetoxy-2-methyl-3-butyne (structure **3** of Scheme I, where $R_1 = R_2$ = methyl) (3.19 g, 25.3 mmol, 1.5 equiv). The reaction mixture was heated to reflux for 18 h. After cooling to rt, the reaction mixture was filtered through a pad of celite and the celite cake was rinsed with EtOAc (300 mL). The filtrate was washed with saturated aqueous NH_4Cl solution (150 mL), H_2O (150 mL) and brine (150 mL). Dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 5 x 20 cm, 5% EtOAc in hexane as eluent) to afford 4.85 g (86%) of compound **101** as a yellow-greenish solid. R_f 0.53 (SiO_2, 10% EtOAc-

hexane). ^{1}H NMR (400 MHz, $CDCl_3$) 7.57 (d, 1H, J = 8.9), 7.19 (s, 1H), 6.95 (d, 1H, J = 8.9), 6.91 (d, 1H, J = 10), 5.50-5.43 (m, 2H), 4.06 (s, 1H), 1.38 (d, 6H, J = 6.2), 1.33 (s, 6H).

EXAMPLE 2

5,6,7,8-Tetrahydro-7,7-dimethyl-2-isopropoxy-4-trifluoromethylpyridino[3,2 -*f*]quinoline (Compound **103**, Structure **5** of Scheme I, where R_1= R_2 = methyl)

In a 250-mL r.b. flask, a solution of compound **101** (3.64g, 10.8 mmol) in TFA (50 mL) was treated with $NaBH_4$ caplets (4.5g, 119 mmol, 11 equiv). The reaction mixture was stirred at rt for 20 h. The reaction mixture was poured onto 200 mL of ice-water, neutralized with $NaHCO_3$ powder to pH 7 and extracted with EtOAc (3 x 250 mL). The combined extracts were washed with brine (2 x 200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 5 x 20 cm, 5% EtOAc in hexane as eluent) to afford 3.38 g (92%) of compound **103** as a yellow solid. R_f 0.50 (SiO_2, 10% EtOAc-hexane). ^{1}H NMR (400 MHz, $CDCl_3$) 7.56 (d, 1H, J = 8.8), 7.24 (s, 1H), 6.89 (d, 1H, J = 8.8), 5.46 (septet, 1H, J = 6.2), 3.85 (s, 1H), 3.07 (t, 2H, J = 6.5), 1.68 (t, 2H, J = 6.5), 1.38 (d, 6H, J = 6.2), 1.26 (s, 6H).

EXAMPLE 3

5,6,7,8-Tetrahydro-7,7-dimethyl-4-trifluoromethylpyridino[3,2-*f*]quinolin-2(1*H*)-one (Compound **104**, Structure **6** of Scheme I, where R_1= R_2 = methyl)

In a 250-mL r.b. flask, a solution of compound **103** (3.97g, 11.7 mmol) in AcOH (50 mL) was treated with conc. HCl (50 mL). The reaction mixture was heated to 95°C and stirred for 4 h. After cooling to rt, the reaction mixture was poured onto ice-water, neutralized with $NaHCO_3$ powder to pH 7 and extracted with EtOAc (3 x 500 mL). The combined extracts were washed with H_2O (500 mL) and brine (500 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by recrystallizing from EtOAc/hexane to afford 3.42 g (98%) of compound **104** as a yellow-orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) 10.35 (br. s, 1H), 7.27 (d, 1H, J = 8.6), 7.25 (s, 1H), 6.82 (d, 1H, J = 8.6), 3.80 (s, 1H), 3.03 (t, 2H, J = 6.5), 1.67 (t, 2H, J = 6.5), 1.24 (s, 6H).

EXAMPLE 4

5,6,7,8-Tetrahydro-7,7-diethyl-4-trifluoromethylpyridino[3,2-*f*]quinolin-2(1*H*)-one (Compound **105**, Structure **6** of Scheme I, where $R_1 = R_2$ = ethyl)

This compound was prepared in a similar fashion as described in Examples 1, 2 and 3 from compound **102** and 2',2'-diethylpropargyl acetate (structure **3** of Scheme I, where $R_1 = R_2$ = ethyl). Spectral data for compound **105**: ^{1}H NMR (400 MHz, $CDCl_3$) 7.22 (s, 1H), 7.14 (d, J = 8.7, 1H), 6.83 (d, J = 8.7, 1H), 3.78 (bs, 1H), 2.98 (t, J = 6.5, 2H), 1.67 (t, J = 6.5, 2H), 1.49 (q, J = 7.4, 6H), 0.89 (t, J = 7.4, 4H).

EXAMPLE 5

7,8-Dihydro-7,7-dimethyl-4-trifluoromethylpyridino[3,2-*f*]quinolin-2(1*H*)-one (Compound **106**, Structure **4a** of Scheme I, where $R_1 = R_2$ = hydrogen)

This compound was prepared in a similar fashion as that described in Example 3 from compound **101**. Spectral data for compound **106**: ^{1}H NMR (500 MHz, acetone-d_6) 11.0 (bs, 1H), 7.24 (d, J = 8.8, 1H), 7.05 (d, J = 8.8, 1H), 6.98 (s, 1H), 6.78 (d, J = 10.3, 1H), 5.62 (bs, 1H), 5.558 (dd, J = 9.8, 1.9, 1H), 1.30 (s, 6H).

EXAMPLE 6

5,6,7,8-Tetrahydro-7,7,8-trimethyl-4-trifluoromethylpyridino[3,2-*f*]quinolin-2(1*H*)-one (Compound **107**, Structure **7** of Scheme I, where $R_1 = R_2 = R_3$ = methyl)

In a 25-mL r.b. flask, a solution of compound **104** (structure **6** of Scheme I, where $R_1 = R_2$ = methyl, 41 mg, 0.15 mmol) in MeOH (5 mL) was treated with formaldehyde (5 mL, 37 wt. % solution in water), AcOH (2 mL) and $NaCNBH_3$ (excess). The reaction mixture was stirred at rt for 24 h. The reaction mixture was poured onto ice-water (50 mL), neutralized with $NaHCO_3$ powder to pH 7 and extracted with EtOAc (3 x 50 mL). The combined extracts were washed with H_2O (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 1 x 20 cm, 50% EtOAc in hexane as eluent) to afford 32 mg (75%) of **107** as an orange solid: R_f 0.40 (SiO_2, 2:1 = EtOAc:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) 11.45 (br. s, 1H), 7.23 (d, 1H, J = 9.1),

7.22 (s, 1H), 7.05 (d, 1H, J = 9.1), 2.97 (t, 2H, J = 6.2), 2.88 (s, 3H), 1.71 (t, 2H, J = 6.2), 1.27 (s, 6H).

EXAMPLE 7

8-Ethyl-5,6,7,8-tetrahydro-7,7-dimethyl-4-trifluoromethylpyridino[3,2-*f*]quinolin-2(1*H*)-one (Compound **108**, Structure **7** of Scheme I, where $R_1 = R_2$ = methyl, R_3 = ethyl)

In a 25-mL r.b. flask, a solution of compound **104** (structure **6** of Scheme I, where $R_1 = R_2$ = methyl) (35.3 mg, 0.119 mmol) in MeOH (5 mL) was treated with acetaldehyde (2 mL), AcOH (2 mL) and $NaCNBH_3$ (excess). The reaction mixture was stirred at rt for 24 h. The reaction mixture was poured onto ice-water (50 mL), neutralized with $NaHCO_3$ powder to pH 7 and extracted with EtOAc (3 x 50 mL). The combined extracts were washed with H_2O (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 1 x 20 cm, 50% EtOAc in hexane as eluent) to afford 19.1 mg (50%) of compound **108** as an orange solid: R_f 0.51 (SiO_2, 2:1 = EtOAc:hexane); ^1H NMR (400 MHz, $CDCl_3$) 11.42 (br. s, 1H), 7.23 (d, 1H, J = 9.2), 7.21 (s, 1H), 7.05 (d, 1H, J = 9.2), 3.38 (q, 2H, J = 7.0), 2.97 (t, 2H, J = 6.2), 1.71 (t, 2H, J = 6.2), 1.27 (s, 6H), 1.17 (t, 3H, J = 7.0).

EXAMPLE 8

5,6,7,8-Tetrahydro-7,7-dimethyl-4-trifluoromethyl-8-propylpyridino[3,2-*f*]quinolin-2(1*H*)-one (Compound **109**, Structure **7** of Scheme I, where $R_1 = R_2$ = methyl, R_3 = propyl)

In a 25-mL r.b. flask, a solution of compound **104** (structure **6** of Scheme I, where $R_1 = R_2$ = methyl) (34 mg, 0.115 mmol) in MeOH (5 mL) was treated with propionaldehyde (2 mL), AcOH (2 mL) and $NaCNBH_3$ (excess). The reaction mixture was stirred at rt for 24 h. The reaction mixture was poured onto ice-water (50 mL), neutralized with $NaHCO_3$ powder to pH 7 and extracted with EtOAc (3 x 50 mL). The combined extracts were washed with H_2O (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 1 x 20 cm, 50% EtOAc in hexane as eluent) to afford 13.2 mg (34%) of compound **109** as an orange solid: R_f 0.51

(SiO_2, 2:1 = EtOAc:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) 10.89 (br. s, 1H), 7.28 (d, 1H, J = 9.0), 7.21 (s, 1H), 7.01 (d, 1H, J = 9.0), 3.20 (t, 2H, J = 7.7), 2.96 (t, 2H, J = 6.1), 1.70 (t, 2H, J = 6.1), 1.60-1.50 (m, 2H), 1.25 (s, 6H), 0.92 (t, 3H, J = 7.3).

EXAMPLE 9

8-(2,2,2-Trifluoroethyl)-5,6,7,8-tetrahydro-7,7-dimethyl-4-trifluoromethyl-pyridino[3,2-*f*]quinolin-2(1*H*)-one (Compound **110**, Structure **7** of Scheme I, where R_1 = R_2 = methyl, R_3 = 2,2,2-trifluoroethyl)

In a 100-mL r.b. flask, a solution of compound **104** (structure **6** of Scheme I, where R_1 = R_2 = methyl) (0.59 g, 2.0 mmol) in TFA (15 mL) was treated with $NaBH_4$ (6.0 g). The reaction mixture was heated to 95°C and stirred for 6 h. The reaction mixture was diluted with EtOAc (50 mL) and poured onto ice-water (50 mL), neutralized with $NaHCO_3$ powder to pH 7 and extracted with EtOAc (2 x 100 mL). The combined extracts were washed with H_2O (150 mL) and brine (150 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 3 x 20 cm, 50% EtOAc in hexane as eluent) to afford 0.62 g (81%) of compound **110** as a yellow solid: R_f 0.56 (SiO_2, 2:1 = EtOAc:hexane); ^{1}H NMR (400 MHz, Acetone-d_6) 11.0 (s, 1H), 7.43 (d, 1H, J = 9.2), 7.35 (d, 1H, J = 9.2), 7.05 (s, 1H), 4.22 (q, 2H, J = 9.0), 2.98 (t, 2H, J = 6.1), 1.77 (t, 2H, J = 6.1), 1.31 (s, 6H).

EXAMPLE 10

6-Hydrazino-4-trifluoromethylquinolin-2(1*H*)-one (Compound **111**, Structure **9** of Scheme II, where R_1 = trifluoromethyl)

In a 250 mL r.b. flask a suspension of 6-amino-4-trifluoromethylquinolin-2(1*H*)-one (structure **8** of Scheme II, where R_1 = trifluoromethyl) (2.28 g, 10 mmol) in 10 mL conc. HCl was cooled to –1°C and a solution of $NaNO_2$ (0.40 g, 12 mmol) in water (5 mL) was added dropwise in 20 min. The dark yellow suspension was stirred at –1°C for 1 h and then a solution of $SnCl_2$•$2H_2O$ (5.2 g, 15 mmol) in conc. HCl (10 mL) was added dropwise in 10 min. The light yellow suspension of the hydrazine was stirred at –1°C for 2 h and then used

directly or kept in a refrigerator at –1°C until it was used (the crude compound can be stored for at least one month without decomposition).

EXAMPLE 11

6-Methyl-4-trifluoromethyl-7H-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **112**, Structure **11** of Scheme II, where R_3 = H, R_2 = methyl, R_1 = trifluoromethyl)

To the crude suspension of compound **111** (~0.4 M) in aqueous HCl was added a solution of acetone (structure **10** of Scheme II, 2-5 eq.) in an equal volume of EtOH and the mixture was heated in a sealed tube at 130°C for 2 h. Then the mixture was diluted with an equal volume of water while still hot and allowed to cool to rt. The precipitate was filtered and washed with water to give compound **112** as a yellow solid: ^{1}H NMR (500 MHz, acetone-d_6) 11.1 (bs, 1 H), 10.6 (bs, 1 H), 7.69 (d, J = 8.8, 1 H), 7.25 (d, J = 8.8, 1 H), 6.94 (s, 1 H), 6.64 (s, 1 H), 2.51 (s, 3 H).

EXAMPLE 12

5-Isopropyl-6-methyl-4-trifluoromethyl-7H-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **113**, Structure **11** of Scheme II, where R_3 = isopropyl, R_2 = methyl, R_1 = trifluoromethyl)

To the crude suspension of compound **111** (structure **9** of Scheme II, where R_1 = trifluoromethyl) (~0.4 M) in aqueous HCl was added a solution of a ketone (structure **10** of Scheme II) (2-5 eq.) in an equal volume of EtOH and the mixture was refluxed for 2 h. Then the mixture was diluted with an equal volume of water while still hot and allowed to cool to rt. The precipitate was filtered and washed with water to give the indole as a mixture of regioisomers. The ratio of angular and linear isomers was determined by ^{1}H NMR. The mixture of regioisomers could be separated by chromatography (Silica gel, hex/EtOAc 1:1 to 0:1 gradient). Spectra data for compound **113**: ^{1}H NMR (500 MHz, DMSO-d_6) 12.2 (bs, 1H), 11.3 (bs, 1H), 7.52 (d, J = 8.8, 1H), 7.03 (d, J = 8.8, 1H), 6.87 (s, 1H), 3.30-3.24 (m, 1H), 6.64 (s, 1H), 2.48 (s, 3H), 1.22 (d, J = 6.8, 6H).

EXAMPLE 13

5-Allyl-6-methyl-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **114**, Structure **11** of Scheme II, where R_3 = allyl, R_2 = methyl, R_1 = trifluoromethyl)

This compound was prepared in a similar fashion as that described in Example 12 from compound **111** (structure **9** of Scheme II, where R_1 = trifluoromethyl) and 5-hexen-2-one (structure **10** of Scheme II) as a yellow solid: ^{1}H NMR (500 MHz, DMSO-d_6) 12.3 (bs, 1H), 11.5 (bs, 1H), 7.59 (d, J = 8.8, 1H), 7.10 (d, J = 8.8, 1H), 6.89 (s, 1H), 5.82-5.76 (m, 1H), 4.85 (dd, J = 10.8, 2.0, 1H), 4.76 (dd, J = 17.1, 2.0, 1H), 3.50 (d, J = 5.9, 2H), 2.33 (s, 3H).

EXAMPLE 14

5-(4-Methoxyphenyl)-6-methyl-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **115**, Structure **11** of Scheme II, where R_3 = 4-methoxyphenyl, R_2 = methyl, R_1 = trifluoromethyl)

This compound was prepared in a similar fashion as that described in Example 12 from compound **111** (structure **9** of Scheme II, where R_1 = trifluoromethyl) and 1-(4-methoxyphenyl)acetone (structure **10** of Scheme II) as a yellow solid: ^{1}H NMR (500 MHz, DMSO-d_6) 12.3 (bs, 1 H), 11.7 (bs, 1 H), 7.64 (d, J = 8.8, 1 H), 7.14 (d, J = 8.8, 1 H), 7.06 (d, J = 8.8, 2 H), 6.91 (d, J = 8.8, 2 H), 6.68 (s, 1 H), 3.77 (s, 3 H), 2.22 (s, 3 H).

EXAMPLE 15

5-(3-Trifluoromethylphenyl)-6-methyl-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **116**, Structure **11** of Scheme II, where R_3 = 3-trifluoromethylphenyl, R_2 = methyl, R_1 = trifluoromethyl)

This compound was prepared in a similar fashion as that described in Example 12 from compound **111** (structure **9** of Scheme II, where R_1 = trifluoromethyl) and 1-(3-trifluoromethylphenyl)acetone (structure **10** of Scheme II) as a yellow solid: ^{1}H NMR (500 MHz, DMSO-d_6) 12.4 (bs, 1H), 11.9 (bs, 1H), 7.69 (d, J = 8.8, 1H), 7.62-7.59 (m, 2H), 7.53 (bd, J = 4.9, 1H), 7.41 (s, 1H), 7.21 (d, J = 8.8, 2H), 6.73 (s, 1 H), 2.27 (s, 3H).

EXAMPLE 16

4-Trifluoromethyl-5,6,7,8-tetrahydrocyclopentano[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **117**, Structure **11** of Scheme II, where R_3, R_2 = $-CH_2CH_2CH_2-$, R_1 = trifluoromethyl

This compound was prepared in a similar fashion as that described in Example 12 from compound **111** (structure **9** of Scheme II, where R_1 = trifluoromethyl) and cyclopentanone (structure **10** of Scheme II) as a yellow solid: ^{1}H NMR (500 MHz, DMSO-d_6) 11.6 (bs, 1H), 10.5 (bs, 1H), 7.73 (d, J = 8.8, 1H), 7.26 (d, J = 8.8, 1H), 6.92 (s, 1H), 3.05-3.02 (m, 2H), 2.91-2.88 (m, 2H), 2.47-2.43 (m, 2H).

EXAMPLE 17

4-Trifluoromethyl-5,6,7,8,9,10-hexahydrocycloheptano[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **118**, Structure **11** of Scheme II, where R_3, R_2 = $-(CH_2)_5-$, R_1 = trifluoromethyl)

This compound was prepared in a similar fashion as that described in Example 12 from compound **111** (structure **9** of Scheme II, where R_1 = trifluoromethyl) and cycloheptanone (structure **10** of Scheme II) as a yellow solid: ^{1}H NMR (500 MHz, DMSO-d_6) 11.4 (bs, 1H), 10.5 (bs, 1H), 7.63 (d, J = 8.3, 1H), 7.17 (d, J = 8.3, 1H), 6.91 (s, 1H), 2.98-2.94 (m, 2 H), 2.91-2.87 (m, 2 H), 1.92-1.86 (m, 2H). 1.81-1.75 (m, 2H), 1.69-1.63 (m, 2H).

EXAMPLE 18

(±)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-(2,2,2-trifluoroethyl)-4-trifluoromethylcyclopentano-[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **119**, Structure **13** of Scheme II, where R_3, R_2 = $-(CH_2)_3-$, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl)

To a solution of compound **117** (structure **11** of Scheme II, where R_3, R_2 = $-(CH_2)_3-$, 1.30 g, 4.45 mmol) in TFA (40 mL) in a 250 mL r.b. flask was added a pellet (~0.75 g, 22 mmol) of $NaBH_4$. Two more pellets of $NaBH_4$ were added with 30 min intervals and the mixture was stirred at rt for 16 h until the starting material was consumed. Water was carefully added (~150 mL) and the yellow precipitate was filtered and washed with water. The yellow solid was purified by column chromatography (Silica gel, hex:EtOAc, 7:3) to give

compound **119** (1.27 g, 76%) as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) 12.3 (bs, 1H), 7.28 (d, J = 8.8, 1H), 7.19 (s, 1H), 6.87 (d, J = 8.8, 1H), 4.30 (d, J = 4.9, 2H), 4.06-4.02 (m, 2H), 3.74-3.58 (m, 2H), 2.15-2.13 (m, 2H), 1.77-1.66 (m, 3H), 1.58-1.53 (m, 1H).

EXAMPLE 19

(±)-6,6a,7,8,9,9a(*cis*)-Hexahydro-6-(2,2,2-trifluoroethyl)-4-trifluoromethylcyclopentano-[i]pyrrolo[2,3-*g*]quinolin-2(1*H*)-one (Compound **120**, Structure **14** of Scheme II, where R_3, R_2 = -$(CH_2)_3$-, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl)

This compound was isolated as a regioisomer of compound **119** (structure **13** of Scheme II, where R_3, R_2 = -$(CH_2)_3$-, R_1 = trifluoromethyl, R_4 = trifluoroethyl) in the same reaction process as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) 12.4 (bs, 1H), 7.18 (s, 1H), 7.03 (s, 1H), 6.64 (s, 1H), 4.35 (dd, J = 6.3, 6.3, 1H), 3.89-3.85 (m, 1H), 3.76 (q, $J_{H\text{-}F}$ = 9.3, 1H), 2.14-2.06 (m, 1H), 1.98-1.92 (m, 1H), 1.888-1.82 (m, 1H), 1.79-1.70 (m, 2H), 1.59-1.53 (m, 1H).

EXAMPLE 20

(±)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-ethyl-4-trifluoromethylcyclopentano-[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **121**, Structure **13** of Scheme II, where R_3, R_2 = -$(CH_2)_3$-, R_1 = trifluoromethyl, R_4 = ethyl)

This compound was prepared in a similar fashion as that described in Example 18 from Compound **117** (structure **11** of Scheme II, where R_3, R_2 = -$(CH_2)_3$-) and acetic acid. ^{1}H NMR (500 MHz, $CDCl_3$) 12.0 (bs, 1H), 7.21 (d, J = 8.3, 1H), 7.19 (s, 1H), 6.87 (d, J = 8.8, 1H), 4.30 (d, J = 4.9, 2H), 4.06-4.02 (m, 2H), 3.74-3.58 (m, 2H), 2.15-2.13 (m, 2H), 1.77-1.66 (m, 3H), 1.58-1.53 (m, 1H).

EXAMPLE 21

(±)-6,6a,7,8,9,9a(*cis*)-Hexahydro-6-ethyl-4-trifluoromethylcyclopentano-[i]pyrrolo[2,3-g]quinolin-2(1*H*)-one (Compound **122**, Structure **14** of Scheme II, where R_3, R_2 = -$(CH_2)_3$-, R_1 = trifluoromethyl, R_4 = ethyl)

This compound was isolated as a regioisomer of compound **121** (Structure **13** of Scheme II, where R_3, R_2 = -$(CH_2)_3$-, R_1 = trifluoromethyl, R_4 = ethyl) in the same reaction described in Example 20 as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) 11.9 (bs, 1H), 7.08 (s, 1H), 6.99 (s, 1 H), 6.41 (d, J = 2.0, 1 H), 4.30-4.27 (m, 1H), 3.79-3.75 (m, 1H), 3.34 (dq, J = 7.3, 7.3, 1H), 3.21 (dq, J = 7.3, 7.3, 1H), 2.08-2.01 (m, 1H), 1.89-1.86 (m, 1H), 1.82-1.79 (m, 1H), 1.72-1.65 (m, 2 H), 1.58-1.52 (m, 1H), 1.18 (t, J = 7.3, 3H).

EXAMPLE 22

(±)-5,6-Dihydro-5,6-*cis*-dimethyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **123**, Structure **13** of Scheme II, where R_3 = R_2 = methyl, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl)

This compound was prepared in a similar fashion as that described in Examples 12 and 18 from Compound **111** (Structure **9** of Scheme II, where R_1 = trifluoromethyl) and 2-butanone. ^{1}H NMR (500 MHz, $CDCl_3$) 12.3 (bs, 1H), 7.32 (d, J = 8.8, 1H), 7.21 (s, 1H), 6.95 (d, J = 8.8, 1H), 3.75-3.53 (m, 4H), 1.38 (d, J = 6.8, 3H), 0.98 (d, J = 6.8, 3H).

EXAMPLE 23

(±)-7,8-Dihydro-7,8-*cis*-dimethyl-6-(2,2,2-trifluoroethyl)-4-trifluoromethyl-6*H*-pyrrolo[2,3-g]quinolin-2(1*H*)-one (Compound **124**, Structure **14** of Scheme II, where R_3 = R_2 = methyl, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl)

This compound was isolated as a regioisomer of compound **123** (Structure **13** of Scheme II, where R_3 = R_2 = methyl, R_1 = trifluoromethyl, R_4 = trifluoroethyl) in the same reaction described in Example 22 as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) 12.1 (bs, 1H), 7.13 (d, J = 1.5, 1H), 7.04 (s, 1H), 6.76 (s, 1H), 3.75-3.60 (m, 2H), 3.33 (dq, J = 6.3, 5.9, 1H), 2.95 (dq, J = 7.3, 5.9, 1H), 1.41 (d, J = 7.3, 3H), 1.39 (d, J = 6.3, 3H).

EXAMPLE 24

(±)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-propyl-4-trifluoromethylcyclopentano-[g]pyrrolo-[3,2-*f*]quinolin-2(1*H*)-one (Compound **125**, Structure **13** of Scheme II, where R_3, R_2 = -$(CH_2)_3$-, R_1 = trifluoromethyl, R_4 = propyl)

This compound was prepared in a similar fashion as that described in Example 18 from Compound **117** (structure **11** of Scheme II, where R_3, R_2 = -$(CH_2)_3$-) and propionic acid. ^{1}H NMR (500 MHz, $CDCl_3$) 10.4 (bs, 1H), 7.31 (dd, J = 8.8, 1.8, 1H), 7.20 (s, 1H), 6.78 (d, J = 8.8, 1H), 4.28-4.26 (m, 1H), 3.96-3.95 (m, 1H), 3.14-3.05 (m, 2H), 2.06-2.03 (m, 2H), 1.72-1.51 (m, 6H), 0.95 (t, J = 7.3, 3H).

EXAMPLE 25

(±)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-(3-furanylmethyl)-4-trifluoromethyl-cyclopentano[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **126**, Structure **13** of Scheme II, where R_3, R_2 = -$(CH_2)_3$-, R_1 = trifluoromethyl, R_4 = 3-furanylmethyl)

This compound was prepared in a similar fashion as that described in Example 18 from Compound **117** (structure **11** of Scheme II, where R_3, R_2 = -$(CH_2)_3$-) and 3-furoic acid. ^{1}H NMR (500 MHz, $CDCl_3$) 12.2 (bs, 1H), 7.36-7.35 (m, 1H), 7.29 (s, 1H), 7.22 (d, J = 8.8, 1H), 7.16 (s, 1 H), 6.82 (d, J = 8.3, 1H), 6.26 (d, J =1.0, 1H), 4.27-4.22 (m, 2H), 4.08 (d, J = 16.1, 1H), 3.97-3.91 (m, 1H), 2.12-2.08 (m, 1H), 2.03-2.01 (m, 1H), 1.72-1.70 (m, 3H), 1.60-1.58 (m, 1H).

EXAMPLE 26

(±)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-(3-thiophenemethyl)-4-trifluoromethyl-cyclopentano[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **127**, Structure **13** of Scheme II, where R_3, R_2 = -$(CH_2)_3$-, R_1 = trifluoromethyl, R_4 = 3-thiophenemethyl)

This compound was prepared in a similar fashion as that described in Example 18 from Compound **117** (structure **11** of Scheme II, where R_3, R_2 = -$(CH_2)_3$-) and 3-thiophenecarboxylic acid. ^{1}H NMR (500 MHz, $CDCl_3$) 10.9 (bs, 1H), 7.29 (dd, J = 5.4, 2.9, 1H), 7.13 (s, 1H), 7.07 (d, J = 8.3, 1H), 7.06 (s, 1H), 6.96 (dd, J = 5.4, 1.5, 1H), 7.12-7.04 (m,

1H), 6.72 (d, J = 8.3, 1H), 4.38 (d, J = 16.1, 1H), 4.26 (d, J = 16.1, 1H), 4.27-4.25 (m, 1H), 3.98-3.94 (m, 1H), 2.16-2.07 (m, 1H), 2.04-2.22 (m, 1H), 1.78-1.68 (m, 3H), 1.60-1.54 (m, 1H).

EXAMPLE 27

(±)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-(2-methylpropyl)-4-trifluoromethyl-cyclopentano[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **128**, Structure **13** of Scheme II, where R_3, R_2 = -$(CH_2)_3$-, R_1 = trifluoromethyl, R_4 = 2-methylpropyl)

This compound was prepared in a similar fashion as that described in Example 18 from Compound **117** (structure **11** of Scheme II, where R_3, R_2 = -$(CH_2)_3$-) and isobutyric acid. ^{1}H NMR (500 MHz, $CDCl_3$) 12.2 (bs, 1H), 7.20 (d, J = 8.8, 1H), 7.15 (s, 1H), 6.74 (d, J = 8.8, 1H), 4.22-4.19 (m, 1H), 3.98-3.93 (m, 1H), 2.93 (dd, J = 14.3, 7.3, 1H), 2.81 (dd, J = 14.3, 7.9, 1H), 2.14-2.00 (m, 3H), 1.72-1.63 (m, 3H), 1.56-1.52 (m, 1 H), 0.97 (d, J = 6.7, 3H), 0.92 (d, J = 6.7, 3H).

EXAMPLE 28

(±)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-(2,2,2-chlorodifluoroethyl)-4-trifluoromethylcyclopentano[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **129**, Structure **13** of Scheme II, where R_3, R_2 = -$(CH_2)_3$-, R_1 = trifluoromethyl, R_4 = 2,2,2-chlorodifluoroethyl)

This compound was prepared in a similar fashion as that described in Example 18 from Compound **117** (structure **11** of Scheme II, where R_3, R_2 = -$(CH_2)_3$-) and chlorodifluoroacetic acid. ^{1}H NMR (500 MHz, $CDCl_3$) 12.3 (bs, 1H), 7.38 (d, J = 8.8, 1 H), 7.29 (s, 1H), 7.00 (d, J = 8.8, 1H), 4.46-4.44 (m, 1H), 4.09-4.05 (m, 1H), 3.94-3.81 (m, 2H), 2.21-2.12 (m, 2H), 1.81-1.74 (m, 2H), 1.69-1.63 (m, 1H), 1.56-1.52 (m, 1 H).

EXAMPLE 29

(±)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-cyclopropylmethyl-4-trifluoromethyl-cyclopentano[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **130**, Structure **13** of Scheme II, where R_3, R_2 = -$(CH_2)_3$-, R_1 = trifluoromethyl, R_4 = cyclopropylmethyl)

This compound was prepared in a similar fashion as that described in Example 18 from Compound **117** (structure **11** of Scheme II, where R_3, R_2 = -$(CH_2)_3$-) and cyclopropanecarboxylic acid. ^{1}H NMR (500 MHz, $CDCl_3$) 12.4 (bs, 1H), 7.25 (d, J = 8.8, 1H), 7.16 (s, 1H), 6.84 (d, J = 8.8, 1H), 4.41-4.38 (m, 1H), 3.97-3.92 (m, 1 H), 3.18 (dd, J = 14.9, 5.5, 1H), 2.90 (dd, J =14.9, 7.3, 1H), 2.14-2.04 (m, 2H), 1.78-1.66 (m, 3H), 1.55-1.49 (m, 1H), 0.97-0.92 (m, 1H), 0.61-0.55 (m, 1H), 0.53-0.47 (m, 1H), 0.28-0.22 (m, 1H), 0.19-0.14 (m, 1H).

EXAMPLE 30

(±)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-(2,2-dimethoxyethyl)-4-trifluoromethyl-cyclopentano[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **131**, Structure **13** of Scheme II, where R_3, R_2 = -$(CH_2)_3$-, R_1 = trifluoromethyl, R_4 = 2,2-dimethoxyethyl)

This compound was prepared in a similar fashion as that described in Example **18** from Compound **117** (structure **11** of Scheme II, where R_3, R_2 = -$(CH_2)_3$-) and dimethoxyacetaldehyde. ^{1}H NMR (500 MHz, $CDCl_3$) 11.1 (bs, 1H), 7.14 (s, 1H), 7.12 (d, J = 8.8, 1H), 6.91 (d, J = 8.8, 1H), 4.43 (dd, J = 5.9, 4.4, 1H), 4.31-4.30 (m, 1H), 3.94-3.93 (m, 1H), 3.41 (s, 6H), 3.30 (dd, J = 15.1, 5.9, 1H), 3.21 (dd, J = 15.1, 4.4, 1H), 2.12-2.09 (m, 2H), 1.72-1.55 (m, 4H).

EXAMPLE 31

(±)-4c,5,6,7,8,8a(*cis*)-Hexahydro-9-(2,2,2-trifluoroethyl)-4-trifluoromethyl-9H-cyclohexano[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **132**, Structure **13** of Scheme II, where R_3, R_2 = -$(CH_2)_4$-, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl)

This compound was prepared in a similar fashion as that described in Examples 12 and 18 from Compound **111** (structure **9** of Scheme II, where R_1 = trifluoromethyl) and

cyclohexanone. ^{1}H NMR (500 MHz, $CDCl_3$) 12.1 (bs, 1H), 7.29 (d, J = 8.8, 1H), 7.19 (s, 1H), 7.02 (d, J = 8.8, 1H), 3.70-3.60 (m, 2H), 3.56 (m, 1H), 3.41-3.38 (m, 1H), 2.14 (d, J = 14.6, 1H), 1.75-1.67 (m, 3H), 1.61-1.56 (m, 2H), 1.31-1.25 (m, 1H), 1.05-0.98 (m, 1H).

EXAMPLE 32

(±)-4c,5,6,7,8,9,9a(*cis*),10-Octahydro-10-(2,2,2-trifluoroethyl)-4-trifluoromethyl-cycloheptano[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **133**, Structure **13** of Scheme II, where R_3, R_2 = -$(CH_2)_5$-, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl)

This compound was prepared in a similar fashion as that described in Example 18 from Compound **118** (structure **11** of Scheme II, where R_3, R_2 = -$(CH_2)_5$-). ^{1}H NMR (500 MHz, $CDCl_3$) 12.0 (bs, 1H), 7.32 (d, J = 8.8, 1H), 7.25 (s, 1H), 6.98 (d, J = 8.8, 1H), 3.96-3.91 (m, 1H), 3.73-3.62 (m, 3H), 2.36-2.26 (m, 2H), 1.93-1.86 (m, 3H), 1.78-1.69 (m, 2H), 1.48-1.36 (m, 3H).

EXAMPLE 33

(±)-5,6- *cis*-Dihydro-6-ethyl-5-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **134**, Structure **13** of Scheme II, where R_3 = methyl, R_2 = ethyl, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl)

This compound was prepared in a similar fashion as that described in Examples 12 and 18 from Compound **111** (structure **9** of Scheme II, where R_1 = trifluoromethyl) and 3-pentanone. ^{1}H NMR (500 MHz, $CDCl_3$) 11.6 (bs, 1H), 7.26 (d, J = 8.3, 1H), 7.15 (s, 1H), 6.74 (d, J = 8.3, 1H), 4.25 (dd, J = 7.3, 3.4, 1H), 3.96-3.91 (m, 1H), 3.29 (dq, J = 7.3, 7.3, 1H), 3.16 (dq, J = 7.3, 7.3, 1H), 1.965-1.85 (m, 2H), 1.08 (t, J = 7.3, 3H), 0.98 (d, J = 6.3, 3H).

EXAMPLE 34

(±)-5,6- *cis*-Dihydro-5-butyl-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **135**, Structure **13** of Scheme II, where R_3 = butyl, R_2 = methyl, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl)

This compound was prepared in a similar fashion as that described in Examples 12 and 18 from Compound **111** (structure **9** of Scheme II, where R_1 = trifluoromethyl) and 2-heptanone. ^{1}H NMR (500 MHz, $CDCl_3$) 12.1 (bs, 1H), 7.29 (d, J = 8.8, 1H), 7.20 (s, 1H), 6.94 (d, J = 8.8, 1H), 3.76-3.68 (m, 1H), 3.67-3.57 (m, 2H), 3.47-3.43 (m, 1H), 1.74-1.66 (m, 1H), 1.44 (d, J = 6.8, 3H), 1.36-1.29 (m, 1H), 1.28-1.20 (m, 1H), 1.20-1.12 (m, 3H), 0.81 (t, J = 7.3, 3 H).

EXAMPLE 35

(±)-5,6- *cis*-Dihydro-5-(4-nitrophenyl)-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **136**, Structure **13** of Scheme II, where R_3 = 4-nitrophenyl, R_2 = methyl, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl)

This compound was prepared in a similar fashion as that described in Examples 12 and 18 from Compound **111** (Structure **9** of Scheme II, where R_1 = trifluoromethyl) and 4-nitrophenylacetone. ^{1}H NMR (500 MHz, $CDCl_3$) 12.1 (bs, 1H), 8.05 (d, J = 8.3, 2H), 7.47 (d, J = 8.8, 1H), 7.13 (d, J = 8.8, 1H), 7.13 (s, 1H), 6.90 (bs, 2H), 4.79 (d, J = 7.3, 1H), 4.11 (dq, J = 7.3, 6.3, 1H), 3.78-3.61 (m, 2H), 0.96 (d, J = 6.3, 3H).

EXAMPLE 36

(±)-5,6- *cis*-Dihydro-5-(4-dimethylaminophenyl)-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **137**, Structure **13** of Scheme II, where R_3 = 4-dimethylaminophenyl, R_2 = methyl, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl)

This compound was prepared in a similar fashion as that described in Examples 12 and 18 from Compound **111** (Structure **9** of Scheme II, where R_1 = trifluoromethyl) and 4-dimethylaminophenylacetone. ^{1}H NMR (500 MHz, $CDCl_3$) 12.3 (bs, 1H), 7.40 (d, J = 8.8,

1H), 7.09 (s, 1H), 7.06 (d, J = 8.8, 1H), 6.56-6.52 (m, 4H), 4.59 (d, J = 7.3, 1H), 3.96 (dq, J = 7.3, 6.3, 1H), 3.77-3.67 (m, 1H), 3.67-3.57 (m, 1H), 2.86 (s, 6H), 0.95 (d, J = 6.3, 3H).

EXAMPLE 37

(±)-5,6- *cis*-Dihydro-5-(4-methoxyphenyl)-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **138**, Structure **13** of Scheme II, where R_3 = 4-methoxyphenyl, R_2 = methyl, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl)

This compound was prepared in a similar fashion as that described in Example 18 from Compound **115** (Structure **11** of Scheme II, where R_3 = 4-methoxyphenyl, R_2 = methyl, R_1 = trifluoromethyl). ^{1}H NMR (500 MHz, $CDCl_3$) 11.6 (bs, 1H), 7.36 (d, J = 8.8, 1H), 7.09 (s, 1H), 7.07 (d, J = 8.8, 1H), 6.71 (d, J = 8.8, 2H), 6.63 (bs, 2H), 4.63 (d, J = 7.3, 1H), 3.99 (dq, J = 7.3, 6.3, 1H), 3.74-3.58 (m, 2H), 3.73 (s, 3H), 0.94 (d, J = 6.3, 3H).

EXAMPLE 38

(±)-5,6- *cis*-Dihydro-5-(3-trifluoromethylphenyl)-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **139**, Structure **13** of Scheme II, where R_3 = 3-trifluoromethylphenyl, R_2 = methyl, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl)

This compound was prepared in a similar fashion as that described in Example 18 from Compound **116** (Structure **11** of Scheme II, where R_3 = 3-trifluoro-methylphenyl, R_2 = methyl, R_1 = trifluoromethyl). ^{1}H NMR (500 MHz, $CDCl_3$) 12.8 (bs, 1H), 7.51 (d, J = 8.8, 1H), 7.43 (d, J = 7.8, 1H), 7.30-7.26 (m, 1H), 7.14 (s, 1H), 7.12 (d, J = 8.8, 1H), 7.12-7.04 (m, 1H), 6.92-6.78 (bs, 1H), 4.74 (d, J = 6.8, 1H), 4.08 (dq, J = 6.8, 6.3, 1H), 3.78-3.60 (m, 2H), 0.93 (d, J = 6.3, 3H).

EXAMPLE 39

(±)-5,6- *cis*-Dihydro-5-(4-fluorophenyl)-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **140**, Structure **13** of Scheme II, where R_3 = 4-fluorophenyl, R_2 = methyl, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl)

This compound was prepared in a similar fashion as that described in Examples 12 and 18 from Compound **111** (Structure **9** of Scheme II, where R_1 = trifluoromethyl) and 4-fluorophenylacetone. ^{1}H NMR (500 MHz, $CDCl_3$) 10.6 (bs, 1H), 7.28 (d, J = 8.8, 1H), 7.08 (s, 1H), 7.07 (d, J = 8.8, 1H), 6.88-6.85 (m, 2H), 6.68 (bs, 2H), 4.66 (d, J = 6.8, 1 H), 4.01 (dq, J = 6.8, 6.3, 1H), 3.73-3.67 (m, 2H), 3.67-3.60 (m, 1H), 0.94 (d, J = 6.3, 3H).

EXAMPLE 40

(±)-5,6-Dihydro-5-phenyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **141**, Structure **13** of Scheme II, where R_3 = phenyl, R_2 = H, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl)

This compound was prepared in a similar fashion as that described in Examples 12 and 18 from Compound **111** (Structure **9** of Scheme II, where R_1 = trifluoromethyl) and phenylacetaldehyde. ^{1}H NMR (500 MHz, $CDCl_3$) 12.6 (bs, 1H), 7.48 (d, J = 8.8, 1H), 7.20-7.14 (m, 3H), 7.14 (s, 1H), 7.05 (d, J = 8.8, 1H), 6.76-6.74 (m, 2H), 4.89 (d, J = 8.3, 2H), 3.93 (dd, J = 8.3, 8.3, 1H), 3.84-3.77 (m, 1H), 3.64-3.56 (m, 1H), 3.55 (d, J = 8.8, 1H).

EXAMPLE 41

(±)-5,6- *cis*-Dihydro-5-(4-methoxyphenyl)-6-methyl-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **142**, Structure **13** of Scheme II, where R_3 = 4-methoxyphenyl, R_2 = methyl, R_1 = trifluoromethyl, R_4 = H)

This compound was isolated as a minor product from the same reaction described in Examples 37. ^{1}H NMR (500 MHz, $CDCl_3$) 12.0 (bs, 1H), 7.32 (d, J = 8.8, 1H), 7.09 (s, 1H), 7.14 (d, J = 8.8, 1H), 7.08 (s, 1H), 6.73 (d, J = 8.8, 2H), 6.65 (bs, 2H), 4.60 (d, J = 7.3, 1H), 4.21 (dq, J = 7.3, 6.3, 1H), 3.73 (s, 3H), 1.25 (bs, 1H), 0.92 (d, J = 6.3, 3H).

EXAMPLE 42

(±)-5,6- *cis*-Dihydro-5-(4-methoxyphenyl)-6-methyl-7-(2,2-dimethoxyethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **143**, Structure **13** of Scheme II, where R_3 = 4-methoxyphenyl, R_2 = methyl, R_1 = trifluoromethyl, R_4 = 2,2-dimethoxyethyl)

This compound was prepared in a similar fashion as that described in Example 30 from Compound **115** (Structure **11** of Scheme II, where R_3 = 4-methoxyphenyl, R_2 = methyl, R_1 = trifluoromethyl). ^{1}H NMR (500 MHz, $CDCl_3$) 11.7 (bs, 1H), 7.33 (d, J = 8.8, 1H), 7.17 (d, J = 8.8, 1H), 7.07 (s, 1H), 6.69 (bd, J = 8.8, 2H), 6.63 (bs, 2H), 4.58 (d, J = 7.3, 1H), 4.31 (dd, J = 5.9, 3.9, 1H), 3.93 (dq, J = 7.3, 6.8, 1H), 3.73 (s, 3H), 3.41 (s, 3H), 3.37 (s, 3H), 3.27 (dd, J = 15.1, 3.9, 1H), 3.22 (dq, J = 15.1, 5.9, 1H), 0.92 (d, J = 6.8, 3H).

EXAMPLE 43

(±)-5,6- *cis*-Dihydro-5-isopropyl-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **144**, Structure **13** of Scheme II, where R_3 = isopropyl, R_2 = methyl, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl)

This compound was prepared in a similar fashion as that described in Example 18 from Compound **113** (Structure **11** of Scheme II, where R_3 = isopropyl, R_2 = methyl, R_1 = trifluoromethyl). ^{1}H NMR (500 MHz, $CDCl_3$) 11.6 (bs, 1H), 7.25 (d, J = 8.3, 1H), 7.17 (s, 1H), 6.93 (d, J = 8.3, 1H), 3.80 (dq, J = 6.8, 6.8, 1H), 3.69-3.52 (m, 2H), 3.40 (dd, J = 6.8, 5.4, 1H), 1.96-1.88(m, 1H), 1.53 (d, J = 6.8, 3H), 0.83 (d, J = 6.8, 1H), 0.79 (d, J = 7.3, 3H).

EXAMPLE 44

(±)-5,6-Dihydro-5-ethyl-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **145**, Structure **13** of Scheme II, where R_3 = ethyl, R_2 = methyl, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl)

This compound was prepared in a similar fashion as that described in Examples 12 and 18 from Compound **111** (Structure **9** of Scheme II, where R_1 = trifluoromethyl) and 2-pentanone. ^{1}H NMR (500 MHz, $CDCl_3$) 12.3 (bs, 1H), 7.29 (d, J = 8.8, 1H), 7.23 (s, 1H), 6.98

(d, J = 8.8, 1H), 3.84-3.78 (m, 1H), 3.71-3.59 (m, 2H), 3.46-3.43 (m, 1H), 1.78-1.70 (m, 2H), 1.47 (d, J = 6.8, 3H), 0.86 (t, J = 7.3, 3H).

EXAMPLE 45

(±)-5,6-Dihydro-5-ethyl-6-propyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **146**, Structure **13** of Scheme II, where R_3 = ethyl, R_2 = propyl, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl)

This compound was prepared in a similar fashion as that described in Examples 12 and 18 from Compound **111** (Structure **9** of Scheme II, where R_1 = trifluoromethyl) and 4-heptanone. ^{1}H NMR (500 MHz, $CDCl_3$) 12.1 (bs, 1H), 7.30 (d, J = 8.8, 1H), 7.19 (s, 1H), 6.95 (d, J = 8.8, 1H), 3.70-3.51 (m, 4H), 1.88-1.53 (m, 4H), 1.47-1.36 (m, 2H), 1.05 (t, J = 7.3, 3H), 0.70 (t, J = 7.3, 3H).

EXAMPLE 46

(±)-5,6-Dihydro-5-(2-ethoxycarbonylethyl)-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **147**, Structure **13** of Scheme II, where R_3 = 2-ethoxycarbonylethyl, R_2 = methyl, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl)

This compound was prepared in a similar fashion as that described in Examples 12 and 18. ^{1}H NMR (500 MHz, $CDCl_3$) 11.6 (bs, 1H), 7.27 (d, J = 8.8, 1H), 7.20 (s, 1H), 6.95 (d, J = 8.8, 1H), 4.01 (q, J = 7.3, 2H), 3.82-3.76 (m, 1H), 3.70-3.58 (m, 2H), 3.56-3.52 (m, 1H), 2.40-2.32 (m, 1H), 2.15-2.08 (m, 1H), 2.05-1.98 (m, 1H), 1.70-1.62 (m, 1H), 1.46 (d, J = 6.4, 3H), 1.18 (t, J = 7.3, 3H).

EXAMPLE 47

6-Ethyl-5-methyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **148**, Structure **11** of Scheme II, where R_3 = methyl, R_2 = ethyl, R_1 = H)

This compound was prepared in a similar fashion as that described in Example 12 from structure **9** of Scheme II (where R_1 = H) and 3-pentanone as a yellow solid: ^{1}H NMR (500 MHz, DMSO-d_6) 11.23 (s, 1H), 8.58 (d, J = 9.5, 1H), 7.56 (d, J = 8.6, 1H), 7.14 (d, J = 8.6, 1H), 6.69 (d, J = 9.5, 1H), 2.76 (q, J = 7.5, 1H), 2.50 (s, 1H), 2.44 (s, 3H), 1.23 (t, J = 7.5, 3H).

EXAMPLE 48

(±)-5,6-*cis*-Dihydro-5-methyl-6-ethyl-7-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **149**, Structure **13** of Scheme II, where R_3 = methyl, R_2 = ethyl, R_1 = H, R_4 = 2,2,2-trifluoroethyl)

This compound was prepared in a similar fashion as that described in Example 18 from Compound **148** (Structure **11** of Scheme II, where R_3 = methyl, R_2 = ethyl, R_1 = H). ^{1}H NMR (500 MHz, $CDCl_3$) 11.16 (s, 1H), 7.75 (d, J = 9.5, 1H), 6.81 (d, J = 8.5, 1H), 6.71 (d, J = 9.6, 1H), 3.60-3.45 (m, 3H), 3.44-3.31 (m, 1H), 1.89-1.75 (m, 2H), 1.11 (d, J = 6.8, 3H), 1.06 (t, J = 7.3, 3H).

EXAMPLE 49

5,6-Dimethyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **150**, Structure **15** of Scheme II, where R_3 = R_2 = methyl, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl)

To a solution of Compound **123** (Structure **13** of Scheme II, where R_3 = R_2 = methyl, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl) (0.35 g, 0.97 mmol) in 30 mL CH_2Cl_2 was added DDQ (0.35 g, 1.5 mmol, 1.5 eq) in small portions. The resulting green mixture was stirred at rt for about 60 min until almost no more starting material was visible on TLC. Then 5% aq. $NaHCO_3$ (30 mL) was added and the mixture was extracted with EtOAc (3 x 50 mL) and the combined organic layers were washed with 5% aq. $NaHCO_3$ (30 mL) and brine, dried

over $MgSO_4$ and concentrated. Purification by chromatography (Silica gel, hexane:EtOAc 2:1 to 0:1 gradient) afforded Compound **150** (195 mg, 56%) as a slightly yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) 11.4 (bs, 1H), 7.55 (d, J = 8.8, 1H), 7.17 (d, J = 8.8, 1H), 7.16 (s, 1H), 4.71 (q, $J_{H\text{-}F}$ = 8.3, 2H), 2.43 (s, 3H), 2.33 (s, 3H).

An alternate oxidation method was also used as described as follow:

To a solution of Compound **123** (10 mg, 0.03 mmol) in 10 mL CH_2Cl_2 was added MnO_2 (approx. 0.3 g, 3.5 mmol, 100 eq) in portions until no more starting material was visible on TLC. Then EtOAc (10 mL) was added and the suspension was filtered through a short pad of celite. The solids were rinsed several times with EtOAc and the combined filtrates were concentrated. Purification by chromatography (Silica gel, hexane:EtOAc 2:1 to 0:1 gradient) afforded Compound **150** as a slightly yellow solid.

EXAMPLE 50

6-Ethyl-5-methyl-7-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **151**, Structure **15** of Scheme II, where R_3 = methyl, R_2 = ethyl, R_1 = H, R_4 = 2,2,2-trifluoroethyl)

This compound was prepared in a similar fashion as that described in Example 49 from Compound **149** (Structure **13** of Scheme II, where R_3 = methyl, R_2 = ethyl, R_1 = H, R_4 = 2,2,2-trifluoroethyl). ^{1}H NMR (500 MHz, $CDCl_3$) 11.20 (s, 1H), 8.54 (d, J = 9.7, 1H), 7.46 (d, J = 8.6, 1H), 7.16 (d, J = 8.7, 1H), 6.77 (d, J = 9.7, 1H), 4.69 (q, J = 8.4, 2H), 2.83 (q, J = 7.6, 2H), 2.56 (s, 3H), 1.23 (t, J = 7.6, 3H).

EXAMPLE 51

6-Methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **152**, Structure **15** of Scheme II, where R_3 = H, R_2 = methyl, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl)

This compound was prepared in a similar fashion as that described in Examples 18 and 49 from Compound **112** (Structure **11** of Scheme II, where R_3 = H, R_2 = methyl, R_1 =

trifluoromethyl). ^{1}H NMR (500 MHz, $CDCl_3$) 11.1 (bs, 1H), 7.92 (d, J = 8.8, 1H), 7.39 (d, J = 8.8, 1H),, 6.99 (s, 1H), 6.80 (s, 1H), 5.18 (q, J_{H-F} = 8.8, 1H), 2.58 (s, 3H).

EXAMPLE 52

6-Ethyl-5-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **153**, Structure **15** of Scheme II, where R_3 = methyl, R_2 = ethyl, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl)

This compound was prepared in a similar fashion as that described in Example 49 from Compound **134** (Structure **13** of Scheme II, where R_3 = methyl, R_2 = ethyl, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl). ^{1}H NMR (500 MHz, $CDCl_3$) 12.2 (bs, 1H), 7.57 (d, J = 8.8, 1H), 7.25 (d, J = 8.8, 1H), 7.18 (s, 1H), 4.62 (q, J_{H-F} = 8.3, 2H), 2.45 (q, J = 7.8, 2H), 2.34 (d, J = 1.9, 3H), 1.24 (t, J = 7.8, 3H).

EXAMPLE 53

5-Ethyl-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **154**, Structure **15** of Scheme II, where R_3 = ethyl, R_2 = methyl, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl)

This compound was prepared in a similar fashion as that described in Example 49 from Compound **145** (Structure **13** of Scheme II, where R_3 = ethyl, R_2 = methyl, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl). ^{1}H NMR (500 MHz, $CDCl_3$) 12.6 (bs, 1H), 7.56 (d, J = 8.8, 1H), 7.28 (d, J = 8.8, 1H), 7.17 (s, 1H), 4.70 (q, J_{H-F} = 8.3, 2H), 2.89 (q, J = 7.3, 2H), 2.46 (s, 3H), 1.01 (t, J = 7.3, 3H).

EXAMPLE 54

5-Ethyl-6-propyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **155**, Structure **15** of Scheme II, where R_3 = ethyl, R_2 = propyl, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl)

This compound was prepared in a similar fashion as that described in Example 49 from Compound **146** (Structure **13** of Scheme II, where R_3 = ethyl, R_2 = propyl, R_1 =

trifluoromethyl, R_4 = 2,2,2-trifluoroethyl). ^{1}H NMR (500 MHz, $CDCl_3$) 11.7 (bs, 1 H), 7.55 (d, J = 8.8, 1H), 7.19 (d, J = 8.8, 1H), 7.15 (s, 1H), 4.71 (q, $J_{H\text{-}F}$ = 8.3, 2H), 2.88 (q, J = 7.3, 2H), 2.79 (t, J = 7.8, 2H), 1.64-1.58 (m, 2H), 1.06 (t, J = 7.3, 3H), 0.98 (t, J = 7.3, 3H).

EXAMPLE 55

5,6,7,8-Tetrahydro-8-trifluoroethyl-4-trifluoromethylcyclopentano[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **156**, Structure **15** of Scheme II, where R_3, R_2 = -$(CH_2)_3$-, R_1 = trifluoromethyl, R_4 = trifluoroethyl)

This compound was prepared in a similar fashion as that described in Example 49 from Compound **119** (Structure **13** of Scheme II, where R_3, R_2 = -$(CH_2)_3$-, R_1 = trifluoromethyl, R_4 = trifluoroethyl). ^{1}H NMR (500 MHz, $CDCl_3$) 11.3 (bs, 1H), 7.57 (d, J = 8.8, 1H), 7.21 (d, J = 8.8, 1H), 7.20 (s, 1H), 4.66 (q, $J_{H\text{-}F}$ = 8.3, 2H), 3.16-3.14 (m, 2H), 2.93-2.90 (m, 2H), 2.53-2.49 (m, 2H).

EXAMPLE 56

8-Trifluoroethyl-4-trifluoromethyl-6,8-dihydrocyclopentano[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **157**, Structure **17** of Scheme II, where R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl)

This compound was isolated as a minor product in the same reaction as that described in Example 55 from Compound **119** (Structure **13** of Scheme II, where R_3, R_2 = -$(CH_2)_3$-, R_1 = trifluoromethyl, R_4 = trifluoroethyl). ^{1}H NMR (500 MHz, $CDCl_3$) 12.2 (bs, 1H), 7.58 (d, J = 9.3, 1H), 7.48 (d, J = 9.3, 1H), 7.30 (s, 1H), 5.16 (s, 1H), 4.67-4.63 (m, 1H), 4.63 (s, 1H), 4.21-4.16 (m, 1H), 2.77 (d, J = 11.2, 1H), 2.65 (d, J = 10.7, 1H).

EXAMPLE 57

9-Trifluoroethyl-4-trifluoromethyl-9*H*-benzo[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **158**, Structure **15** of Scheme II, where R_3, R_2 = -$(CH{=}CH)_2$-, R_1 = trifluoromethyl, R_4 = trifluoroethyl)

This compound was prepared in a similar fashion as that described in Example 49 from Compound **132** (Structure **13** of Scheme II, where R_3, R_2 = -$(CH_2)_4$-, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl). ^{1}H NMR (500 MHz, $CDCl_3$) 11.4 (bs, 1H), 8.39 (d, J = 8.8, 1H), 8.19 (d, J = 8.8, 1H), 7.82 (d, J = 8.3, 1H), 7.76 (d, J = 9.3, 1H), 7.57 (t, J = 7.3, 1H), 7.34 (t, J = 8.3, 1H), 7.21 (s, 1H), 5.46 (q, $J_{H\text{-}F}$ = 8.3, 2H).

EXAMPLE 58

6-Trifluoroethyl-4-trifluoromethyl-6,7,8,9-tetrahydrocyclopetano[*i*]pyrrolo[2,3-*g*]quinolin-2(1*H*)-one (Compound **159**, Structure **16** of Scheme II, where R_3, R_2 = -$(CH_2)_3$-, R_1 = trifluoromethyl, R_4 = trifluoroethyl)

This compound was isolated as a regioisomer of Compound **156** in Example 49. ^{1}H NMR (500 MHz, $CDCl_3$) 10.8 (bs, 1H), 7.84 (s, 1H), 7.47 (s, 1H), 6.81 (s, 1H), 5.13 (q, $J_{H\text{-}F}$ = 9.3, 1H), 3.06-3.00 (m, 2H), 2.62-2.56 (m, 2H).

EXAMPLE 59

5-(3-Trifluoromethylphenyl)-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **160**, Structure **15** of Scheme II, where R_3 = 3-trifluoromethylphenyl, R_2 = methyl, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl)

This compound was prepared in a similar fashion as that described in Example 49 from Compound **139** (Structure **13** of Scheme II, where R_3 = 3-trifluoromethylphenyl, R_2 = methyl, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl). ^{1}H NMR (500 MHz, $CDCl_3$) 12.8 (bs, 1H), 7.65 (d, J = 8.8, 1H), 7.60 (d, J = 8.3, 1H), 7.53 (dd, J = 8.3, 8.3, 1H), 7.46 (s, 1H), 7.45 (d, J = 8.3, 1H), 7.39 (d, J = 8.8, 1H), 7.00 (s, 1H), 4.78 (q, $_{JH\text{-}F}$ = 8.3, 2H), 2.33 (s, 3H).

EXAMPLE 60

5-(4-Fluorophenyl)-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **161**, Structure **15** of Scheme II, where R_3 = 4-fluorophenyl, R_2 = methyl, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl)

This compound was prepared in a similar fashion as that described in Example 49 from Compound **140** (Structure **13** of Scheme II, where R_3 = 4-fluorophenyl, R_2 = methyl, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl). ^{1}H NMR (500 MHz, $CDCl_3$) 11.1 (bs, 1H), 7.98 (d, J = 8.8, 1H), 7.40 (d, J = 8.8, 1H), 7.29 (dd, J = 8.8, 5.4, 1H), 7.16 (dd, J = 8.8, 8.3, 1H), 6.76 (s, 1H), 5.26 (q, $J_{H\text{-}F}$ = 8.8, 2H), 2.38 (s, 3H).

EXAMPLE 61

5-(2-Ethoxycarbonylethyl)-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **162**, Structure **15** of Scheme II, where R_3 = 2-ethoxycarbonylethyl, R_2 = methyl, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl)

This compound was prepared in a similar fashion as that described in Example 49 from Compound **147** (Structure **13** of Scheme II, where R_3 = 2-ethoxycarbonylethyl, R_2 = methyl, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl). ^{1}H NMR (500 MHz, $CDCl_3$) 11.7 (bs, 1H), 7.55 (d, J = 8.3, 1H), 7.21 (d, J = 8.8, 1H), 7.17 (s, 1H), 4.71 (q, $J_{H\text{-}F}$ = 7.8, 2H), 3.94 (q, J = 7.3, 2H), 3.24 (t, J =7.3, 2H), 2.49 (s, 3H), 2.38 (t, J = 7.3, 3H), 1.07 (t, J = 7.3, 3H).

EXAMPLE 62

7-Ethyl-8-methyl-6-(2,2,2-trifluoroethyl)-4-trifluoromethyl-6*H*-pyrrolo[2,3-*g*]quinolin-2(1*H*)-one (Compound **163**, Structure **16** of Scheme II, where R_3 = ethyl, R_2 = methyl, R_1 = trifluoromethyl, R_4 = 2,2,2-trifluoroethyl)

This compound was a regioisomer of Compound **153** and prepared in a similar fashion as that described in Example 52. ^{1}H NMR (500 MHz, $CDCl_3$) 9.4 (bs, 1H), 7.68 (s, 1H), 7.25 (s, 1H), 6.99 (s, 1H), 4.69 (q, $J_{H\text{-}F}$ = 8.3, 2H), 2.85 (q, J = 7.8, 2H), 2.30 (s, 3H), 1.25 (t, J = 7.8, 3H).

EXAMPLE 63

5-Hydroxymethyl-6-ethyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **164**, Structure **19** of Scheme III, where R_3 = hydroxymethyl, R_4 = ethyl, R_5 = 2,2,2-trifluoroethyl)

This compound was prepared by the general oxidation procedure described in Example **49** from Compound **153** (Structure **18** of Scheme III, where R_2 = ethyl). ^{1}H NMR (500 MHz, $CDCl_3$) 12.4 (bs, 1H), 7.84 (d, J = 8.8, 1H), 7.24 (d, J = 8.8, 1H), 7.02 (s, 1H), 5.10 (q, J_{H-F} = 8.8, 2H), 4.92 (s, 2H), 4.85 (bs, 1H), 3.00 (q, J = 7.3, 2H), 1.29 (t, J = 7.3, 3H).

EXAMPLE 64

5-Methyl-6-(1-hydroxyethyl)-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **165**, Structure **19** of Scheme III, where R_3 = methyl, R_4 = 1-hydroxyethyl, R_5 = 2,2,2-trifluoroethyl)

This compound was prepared by the general oxidation procedure described in Example 49 from Compound **153** (Structure **18** of Scheme III, where R_2 = ethyl). ^{1}H NMR (500 MHz, $CDCl_3$) 11.2 (bs, 1H), 7.89 (d, J = 8.8, 1H), 7.33 (d, J = 8.8, 1H), 6.96 (s, 1H), 5.63-5.54 (m, 1H), 5.49-5.44 (m, 1H), 5.37-5.28 (m, 1H), 4.81-4.77 (m, 1H), 2.37 (d, J = 2.4, 3H), 1.62 (d, J = 6.8, 3H).

EXAMPLE 65

5-Methyl-6-acetyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **166**, Structure **19** of Scheme III, where R_3 = methyl, R_4 = acetyl, R_5 = 2,2,2-trifluoroethyl)

This compound was isolated as an over oxidized product in Example 64. ^{1}H NMR (500 MHz, $CDCl_3$) 10.5 (bs, 1H), 7.64 (d, J = 8.8, 1H), 7.31 (s, 1H), 7.20 (d, J = 8.8, 1H), 5.39 (q, J_{H-F} = 7.8, 2H), 2.72 (s, 3H), 2.64 (s, 3H).

EXAMPLE 66

5-Formyl-6-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **167**, Structure **19** of Scheme III, where R_3 = formyl, R_4 = methyl, R_5 = 2,2,2-trifluoroethyl)

This compound was prepared by the general oxidation procedure described in Example 49 from Compound **150** (Structure **18** of Scheme III, where $R_1 = R_2$ = methyl). ^{1}H NMR (500 MHz, $CDCl_3$) 11.9 (bs, 1H), 10.16 (d, J = 1.5, 1H), 8.04 (d, J = 8.8, 1H), 7.49 (d, J = 8.8, 1H), 7.00 (s, 1H), 5.37 (q, J_{H-F} = 8.8, 2H), 2.85 (s, 3H).

EXAMPLE 67

5-Acetyloxymethyl-6-ethyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **168**, Structure **20** of Scheme III)

In a 50 mL r.b. flask, a solution of 30 mg (0.08 mmol) of Compound **164** (Structure **19** of Scheme III, where R_3 = hydroxymethyl, R_4 = ethyl, R_5 = 2,2,2-trifluoroethyl) in 10 mL THF was treated with triethylamine (0.5 mL, 3.5 mmol, 40 eq) followed by acetic anhydride (0.2 mL, 2 mmol, 25 eq) and DMAP (1 mg, 0.008 mmol, 0.1 eq). The mixture was stirred at rt for 2 h and then 30 mL 2N HCl and 20 mL EtOAc added and vigorously stirred for 1 h. The layers were separated and the water layer was extracted with EtOAc (20 mL). The combined organic layers were washed with 20 mL portions of 2N HCl, water, 2N NaOH and brine and dried over $MgSO_4$. Concentration followed by purification by flash chromatography (hexane: EtOAc 5:1 to 0:1 gradient) afforded Compound **168**. ^{1}H NMR (500 MHz, $CDCl_3$) 11.1 (bs, 1H), 7.54 (d, J = 8.8, 1H), 7.25 (d, J = 8.8, 1H), 7.13 (s, 1H), 4.73 (q, J_{H-F} = 8.3, 2H), 4.68 (s, 2H), 3.26 (s, 3H), 2.92 (q, J = 7.3, 2H), 1.27 (t, J = 7.3, 3H).

EXAMPLE 68

2-Acetyloxy-5-hydroxymethyl-6-ethyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinoline (Compound **169**, Structure **23** of Scheme III)

This compound was prepared by treatment of Compound **164** (Structure **19** of Scheme III, where R_3 = hydroxymethyl, R_4 = ethyl, R_5 = 2,2,2-trifluoroethyl) with acetic anhydride in

Example 67. ^{1}H NMR (500 MHz, $CDCl_3$) 7.79 (s, 2 H), 7.57 (s, 1H), 4.98 (s, 2H), 4.82 (q, J_{H-F} = 8.3, 2H), 3.03 (q, J = 7.8, 2H), 2.43 (s, 3H), 1.33 (t, J = 7.8, 3H).

EXAMPLE 69

6-Ethyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **170**, Structure **21** of Scheme III)

This compound was isolated as a by-product in the treatment of Compound **164** (Structure **19** of Scheme III, where R_3 = hydroxymethyl, R_4 = ethyl, R_5 = 2,2,2-trifluoroethyl) with acetic anhydride in Example 67. ^{1}H NMR (500 MHz, $CDCl_3$) 11.2 (bs, 1H), 7.94 (d, J = 8.8, 1H), 7.39 (d, J = 8.8, 1H), 7.00 (s, 1H), 6.82 (d, J = 2.0, 1H), 5.19 (q, J_{H-F} = 8.8, 2H), 2.94 (q, J = 7.3, 2H), 1.42 (t, J = 7.3, 3H).

EXAMPLE 70

5-Ethoxymethyl-6-ethyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **171**, Structure **20** of Scheme III)

This compound was isolated as a by-product in the treatment of Compound **164** (Structure **19** of Scheme III, where R_3 = hydroxymethyl, R_4 = ethyl, R_5 = 2,2,2-trifluoroethyl) with acetic anhydride in Example 67. ^{1}H NMR (500 MHz, $CDCl_3$) 11.3 (bs, 1H), 7.92 (d, J = 8.8, 1H), 7.34 (d, J = 8.8, 1H), 6.95 (s, 1H), 5.22 (q, J_{H-F} = 8.8, 2H), 4.72 (s, 2H), 3.37 (q, J = 6.8, 2H), 3.00 (q, J = 7.3, 2H), 1.29 (t, J = 7.3, 3H), 1.07 (t, J = 6.8, 3H).

EXAMPLE 71

6-(1-Methoxyethyl)-5-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **172**, Structure **22** of Scheme III)

In a 50 mL r.b. flask, a solution of 5 mg (0.01 mmol) of Compound **165** (Structure **19** of Scheme III, where R_3 = methyl, R_4 = 1-hydroxyethyl, R_5 = 2,2,2-trifluoroethyl) in 5 mL MeOH was treated with aqueous 2.5 N HCl (2 mL, 5 mmol). The mixture was stirred at rt for 20 h and then 30 mL water was added and the water layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine and dried over $MgSO_4$.

Concentration followed by purification by flash chromatography (hexane: EtOAc 2:1 to 1:1 gradient) afforded 4.2 mg of Compound **172** as a slightly yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) 13.2 (bs, 1H), 7.64 (d, J = 8.8, 1H), 7.39 (d, J = 8.8, 1H), 7.20 (s, 1H), 5.27-5.20 (m, 1H), 4.69-4.85 (m, 2H), 3.25 (s, 3H), 2.37 (d, J = 1.8, 3H), 1.63 (d, J = 7.0, 3H).

EXAMPLE 72

7-Allyl-6-methyl-4-trifluoromethyl-5*H*-pyrrolo[2,3-*f*]quinolin-2(1*H*)-one (Compound **173**, Structure **26** of Scheme IV, where R_2 = methyl, R_3 = allyl)

In a 250 mL r.b. flask a suspension of 5-amino-4-trifluoromethylquinolin-2-one (Structure **24** of Scheme IV) (42 mg, 0.18 mmol) in 4 mL conc. HCl was cooled to –1°C and a solution of $NaNO_2$ (20 mg, 0.6 mmol) in water (0.5 mL) was added dropwise in 1 min. The dark brown suspension was stirred at –1°C for 1 h and then a solution of $SnCl_2 \cdot 2H_2O$ (0.20 g, 0.6 mmol) in conc. HCl (1 mL) was added dropwise in 1 min. The light yellow suspension of Compound **174** (Structure **25** of Scheme IV) was stirred at –1°C for 30 min and then kept in a refrigerator at –1°C for 3 days. To the crude suspension of the hydrazine was added a solution of 5-hexen-2-one (0.1 mL, 0.9 mmol, 5 eq) in 5 mL of EtOH and the mixture was refluxed for 3 h. Then the mixture was diluted with 30 mL of water and extracted with EtOAc (2 x 30 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. Purification by chromatography (Silica gel, hex:EtOAc 3:1) afforded Compound **173** as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) 11.1 (bs, 1H), 9.3 (bs, 1H), 7.80 (d, J = 8.3, 1H), 7.26 (d, J = 8.3, 1H), 6.95 (s, 1H), 6.02-5.95 (m, 1H), 5.05 (dd, J = 17.1, 2.0, 1H), 4.97 (dd, J = 9.8, 2.0, 1H), 3.50 (d, J = 6.3, 1H), 2.46 (s, 3H).

EXAMPLE 73

6-Ethyl-7-methyl-4-trifluoromethyl-5*H*-pyrrolo[2,3-*f*]quinolin-2(1*H*)-one (Compound **175**, Structure **26** of Scheme IV, where R_2 = ethyl, R_3 = methyl)

This compound was prepared in a similar fashion as that described in Example 72 from Compound **174** (Structure **25** of Scheme IV) and 3-pentanone. ^{1}H NMR (500 MHz,

$CDCl_3$) 11.2 (bs, 1H), 9.1 (bs, 1H), 7.79 (d, J = 8.3, 1H), 7.27 (d, J = 8.8, 1H), 6.96 (s, 1H), 2.87 (q, J = 7.8, 2H), 2.27 (s, 1H), 1.27 (t, J = 7.8, 3H).

EXAMPLE 74

7-(3-Trifluoromethylphenyl)-6-methyl-4-trifluoromethyl-5*H*-pyrrolo[2,3-*f*]quinolin-2(1*H*)-one (Compound **176**, Structure **26** of Scheme IV, where R_2 = methyl, R_3 = 3-trifluoromethylphenyl)

This compound was prepared in a similar fashion as that described in Example 72 from Compound **174** (Structure **25** of Scheme IV) and 3-trifluorophenylacetone. ^{1}H NMR (500 MHz, $CDCl_3$) 12.9 (bs, 1H), 8.9 (bs, 1H), 7.90 (d, J = 8.8, 1H), 7.71 (s, 1H), 7.64 (s, 3H), 7.30 (d, J = 8.8, 1H), 7.29 (s, 1H), 2.59(s, 3H).

EXAMPLE 75

7-(2-Hydroxyethyl)-6-methyl-4-trifluoromethyl-5*H*-pyrrolo[2,3-*f*]quinolin-2(1*H*)-one (Compound **177**, Structure **26** of Scheme IV, where R_2 = methyl, R_3 = 2-hydroxyethyl)

This compound was prepared in a similar fashion as that described in Example 72 from Compound **174** (Structure **25** of Scheme IV) and 5-hydroxy-2-pentanone. ^{1}H NMR (500 MHz, $CDCl_3$) 11.3 (bs, 1H), 9.4 (bs, 1H), 7.89 (d, J = 8.5, 1H), 7.29 (d, J = 8.5, 1H), 6.97 (d, J = 0.6, 1H), 3.78 (t, J = 7.3, 2H), 3.23 (t, J = 7.3, 2H), 2.51 (s, 3H).

EXAMPLE 76

(+)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-trifluoroethyl-4-trifluoromethylcyclopentano-[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **178**, Structure **13** of Scheme II, where R_3, R_2 = -$(CH_2)_3$-, R_1 = trifluoromethyl, R_4 = trifluoroethyl) and (–)-4c,5,6,7,7a(*cis*),8-Hexahydro-8-trifluoroethyl-4-trifluoromethylcyclopentano-[g]pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **179**, Structure **13** of Scheme II, where R_3, R_2 = -$(CH_2)_3$-, R_1 = trifluoromethyl, R_4 = trifluoroethyl)

Compounds **178** and **179** were enantiomers of Compound **119** and separated by chiral HPLC.

EXAMPLE 77

4-Trifluoromethyl-6,7-dihydro-7,7,9-trimethyl-pyrido[2,3-*g*]quinolin-2(1*H*)-one (Compound **180**, Structure **28** of Scheme V, where R_1 = trifluoromethyl)

A mixture of Compound **181** (Structure **8** of Scheme V, where R_1 = trifluoromethyl), iodine and acetone in a sealed tube was heated at 135°C overnight and the mixture was concentrated. Chromatography of the crude mixture afforded Compound **180** as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) 7.21 (s, 1H), 6.83 (m, 1H), 6.77 (s, 1H), 5.68 (s, 1H), 5.46 (bs, 1H), 2.02 (s, 3H) and 1.31 (s, 6H).

EXAMPLE 78

8-(2,2,2-Trifluoroethyl)-5,6,7,8-tetrahydro-5,7,7-trimethylpyrido[3,2-*f*]quinolin-2(1*H*)-one (Compound **182**, Structure **29** of Scheme V, where R_1 = H)

A mixture of Compound **183** (Structure **8** of Scheme V, where R_1 = H), iodine and acetone in a sealed tube was heated at 135°C overnight and the mixture was concentrated. Chromatography of the crude mixture afforded Compound **184** (Structure **27** of Scheme V, where R_1 = H) as a yellow solid.

Compound **184** was treated with TFA and $NaBH_4$ in a similar fashion as that described in Example 18 to afford Compound **182** as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) 11.29 (s, 1H), 7.96 (d, J = 9.9, 1H), 7.15 (d, J = 9.1, 1H), 7.06 (d, J = 9.1, 1H), 6.69 (d, J = 9.8, 1H), 3.84 (q, J = 8.7, 2H), 3.41- 3.47 (m, 1H), 2.08 (dd, J = 13.6, 7.3, 1H), 1.88 (dd, J= 13.6, 7.3, 1H), 1.39 (s, 3H), 1.35 (d, J = 6.7, 3H), 1.08 (s, 3H).

EXAMPLE 79

4,5,7-Tri(trifluoromethyl)pyrido[3,2-*f*]quinolin-2(1*H*)-one (Compound **185**, Structure **30** of Scheme V, where R_1 = trifluoromethyl)

A mixture of Compound 181 and 1,1,1,5,5,5-hexafluoro-2,4-pentadiene was heated to 170°C for 2 h and was poured into ice-water. The crude mixture was extracted with EtOAc and the combined organic phase was concentrated. Chromatography provided Compound

185 as a white solid. ^{1}H NMR (400 MHz, acetone-d_6) 11.15 (s, 1H), 8.25 (s, 1H), 8.04 (d, J = 9.0, 1H), 7.58 (d, J = 9.0, 1H), 6.99 (s, 1H).

EXAMPLE 80

5,7-Bis(trifluoromethyl)pyrido[3,2-*f*]quinolin-2(1*H*)-one (Compound **186**, Structure **30** of Scheme V, where R_1 = H)

This compound was prepared in a similar fashion as that described in Example 79 from Compound **183** (Structure **8** of Scheme V, where R_1 =H) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) 12.49 (s, 1H), 8.60 (d, J = 9.9, 1H), 8.28 (d, J = 9.4, 1H), 8.19 (s, 1H), 7.99 (d, J = 9.4, 1H), 6.79 (d, J = 9.9, 1H).

EXAMPLE 81

4-Trifluoromethyl-7-methyl-6,7,8,9-tetrahydropyrido[2,3-*g*]quinolin-2(1*H*)-one (Compound **187**, Structure **33** of Scheme VI, where R_1 = methyl, n = 1)

Preparation of 1-acetyl-2-methyl-6-nitrotetrahydroquinoline (Compound **188**, Structure **32** of Scheme VI, where R_1 = methyl, n = 1)

In a 100-mL r.b. flask, a solution of Compound **189** (Structure 31 of Scheme VI, where R_1 = methyl, n = 1) (1.56 g, 8.2 mmol) in 1,2-dichloroethane (15 mL) was treated with $Yb(OTf)_3$ (0.622 g, 1.0 mmol, 12 mol%) and fuming nitric acid (2.0 mL, 47.0 mmol, 5.7 equiv). The reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with H_2O (50 mL) and brine (50 mL). Dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 4 x 20 cm, 25% EtOAc/hexane as eluent) to afford 1.22 g (63%) of Compound **188** as white solid. R_f 0.45 (SiO_2 ' 50% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$) 8.10-8.00 (m, 2H), 7.44 (d, 1H, J = 8.5), 4.76 (sixtet, 1H, J = 6.6), 2.85-2.79 (m, 1H), 2.74-2.68 (m, 1H), 2.38-2.30 (m, 1H), 2.24 (s, 3H), 1.58-1.54 (m, 1H), 1.18 (d, 3H, J = 6.6).

4-Trifluoromethyl-7-methyl-6,7,8,9-tetrahydropyrido[2,3-*g*]quinolin-2(1*H*)-one (Compound **187**, Structure **33** of Scheme VI, where R_1 = methyl, n = 1)

In a 100-mL r.b. flask, a solution of Compound **188** (1.22 g, 5.2 mmol) in a 1:1 mixture of CH_2Cl_2/EtOH (30 mL) was treated with 10% Pd/C (140 mg, 11 wt % equiv). The reaction mixture was stirred under hydrogen (1 atm) at rt for 18 h. The reaction mixture was filtered through a pad of celite and rinsed with CH_2Cl_2 (100 mL). The filtrate was concentrated to give 1.02 g (96%) of the corresponding amine which was used immediately in the next reaction without further purification.

In a 100-mL r.b. flask, a solution of the amine (1.02 g, 5.0 mmol) in a 95:5 mixture of toluene/water (30 mL) was heated to reflux for 16 h. After cooling to rt, the reaction mixture was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was then dissolved in 20 mL conc. H_2SO_4 and heated to 95°C for 4 h. The reaction mixture was cooled to rt and poured onto 200 mL of ice-water, neutralized with 6N NaOH to pH 7 and extracted with EtOAc (3 x 250 mL). The combined extracts were washed with brine (2 x 200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 3 x 20 cm, 50-70% EtOAc in hexane gradient eluent) to afford 0.21 g (15%) of Compound **187** as a yellow solid. R_f 0.30 (SiO_2, 2:1 = EtOAc:hexane). ^{1}H NMR (400 MHz, $CDCl_3$) 11.70 (s, 1H), 7.11 (s, 1H), 7.00 (s, 1H), 6.80 (s, 1H), 4.02 (br. s, 1H), 3.48-3.43 (m, 1H), 2.95-2.91 (m, 2H), 2.01-1.96 (m, 1H), 1.25 (d, 3H, J = 6.1), 0.89-0.85 (m, 1H).

EXAMPLE 82

4-Trifluoromethyl-7,8-dihydro-6*H*-pyrrolo[2,3-*g*]quinolin-2(1*H*)-one (Compound **190**, Structure **33** of Scheme VI, where R_1 = H, n = 0)

This compound was prepared in a similar fashion as that described in Example 81 from Compound **191** (Structure **31** of Scheme VI, where R_1 = H, n = 0). ^{1}H NMR (acetone-d_6) 7.28 (s, 1H), 6.82 (s, 2H), 5.25 (bs, 1H), 3.60 (t, J = 8.2, 2H), 3.12 (t, J = 8.2, 2H).

EXAMPLE 83

4-Trifluoromethyl-5,6,7,8-tetrahydropyrido[2,3-*g*]quinolin-2(1*H*)-one (Compound **192**, Structure **33** of Scheme VI, where R_1 = H, n = 1)

This compound was prepared in a similar fashion as that described in Example 81 from Compound **193** (Structure **31** of Scheme VI, where R_1 = H, n = 1). ^{1}H NMR (400 MHz, $CDCl_3$) 11.18 (s, 1H), 7.09 (s, 1H), 7.00 (s, 1H), 6.80 (s, 1H), 4.08 (s, 1H), 3.35 (t, 2H, *J* = 5.4), 2.91 (t, 2H, *J* = 6.4), 1.97 (m, 2H).

EXAMPLE 84

4-Trifluoromethyl-7-methyl-6-propyl-6,7,8,9-tetrahydropyrido[2,3-*g*]quinolin-2(1*H*)-one (Compound **194**, Structure **34** of Scheme VI, where R_1 = methyl, R_2 = propyl, n = 1)

In a 25-mL r.b. flask, a solution of Compound **187** (Structure **33** of Scheme VI, where R_1 = methyl, n = 1) (12.2 mg, 0.043 mmol) in MeOH (5 mL) was treated with propionaldehyde (2 mL), AcOH (2 mL) and $NaCNBH_3$. The reaction mixture was stirred at rt for 18 h. The reaction mixture was poured onto ice-water (50 mL), neutralized with $NaHCO_3$ to pH 7 and extracted with EtOAc (3 x 50 mL). The combined extracts were washed with H_2O (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 50% EtOAc/hexane as eluent) to afford 5.0 mg (34%) of Compound **194** as a yellow solid. R_f 0.51 (SiO_2, 2:1 = EtOAc:hexane). ^{1}H NMR (400 MHz, $CDCl_3$) 11.45 (br. s, 1H), 7.09 (s, 1H), 7.00 (s, 1H), 6.75 (s, 1H), 3.55 (m, 1H), 3.35-3.29 (m, 1H), 3.21-3.12 (m, 1H), 2.95-2.80 (m, 2H), 2.00-1.78 (m, 2H), 1.72-1.60 (m, 1H), 1.17 (d, 3H, *J* = 6.5), 0.97 (t, 3H, *J* = 7.3), 0.89-0.85 (m, 1H).

EXAMPLE 85

4-Trifluoromethyl-7-methyl-6-cyclopropylmethyl-6,7,8,9-tetrahydropyrido[2,3-*g*]quinolin-2(1*H*)-one (Compound **195**, Structure **34** of Scheme VI, where R_1 = methyl, R_2 = cyclopropylmethyl, n = 1)

This compound was prepared in a similar fashion as that described in Example 84 from Compound **187** (Structure **33** of Scheme VI, where R_1 = methyl, n =1) and cyclopropanecarboxaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$) 10.91 (br. s, 1H), 7.14 (s, 1H), 7.01 (s, 1H), 6.94 (s, 1H), 3.65 (m, 1H), 3.35 (dd, 1H, *J* = 15.0, 5.5), 3.09 (dd, 1H, *J* = 15.0, 6.2), 2.97-2.82 (m, 2H), 2.00-1.94 (m, 1H), 1.84-1.79 (m, 1H), 1.17 (d, 3H, *J* = 6.5), 0.88-0.85 (m, 1H), 0.58 (m, 2H), 0.28 (dd, 2H, *J* = 10.3, 5.0).

EXAMPLE 86

4-Trifluoromethyl-7-methyl-6-ethyl-6,7,8,9-tetrahydropyrido[2,3-*g*]quinolin-2(1*H*)-one (Compound **196**, Structure **34** of Scheme VI, where R_1 = methyl, R_2 = ethyl, n = 1)

This compound was prepared in a similar fashion as that described in Example 84 from Compound **187** (Structure **33** of Scheme VI, where R_1 = methyl, n =1) and acetaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$) 11.19 (br. s, 1H), 7.11 (s, 1H), 7.00 (s, 1H), 6.80 (s, 1H), 3.55 (m, 1H), 3.47-3.32 (m, 2H), 2.93-2.80 (m, 2H), 1.93-1.79 (m, 2H), 1.22 (t, 3H, J = 7.0), 1.18 (d, 3H, J = 6.4).

EXAMPLE 87

4-Trifluoromethyl-7-methyl-6-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydropyrido[2,3-*g*]quinolin-2(1*H*)-one (Compound **197**, Structure **34** of Scheme VI, where R_1 = methyl, R_2 = 2,2,2-trifluoroethyl, n = 1)

This compound was prepared in a similar fashion as that described in Example 84 from Compound **187** (Structure **33** of Scheme VI, where R_1 = methyl, n =1) and trifluoroacetaldehyde ethyl hemiacetal. ^{1}H NMR (400 MHz, $CDCl_3$) 11.08 (br. s, 1H), 7.06 (s, 1H), 7.00 (s, 1H), 6.99 (s, 1H), 3.99 (m, 1H), 3.81 (m, 1H), 3.67 (m, 1H), 3.10-2.95 (m, 1H), 2.92-2.82 (m, 1H), 2.07-1.97 (m, 1H), 1.93-1.80 (m, 1H), 1.19 (d, 3H, J = 6.5).

EXAMPLE 88

4-Trifluoromethyl-6-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydropyrido[2,3-*g*]quinolin-2(1*H*)-one (Compound **198**, Structure **34** of Scheme VI, where R_1 = H, R_2 = 2,2,2-trifluoroethyl, n = 1)

This compound was prepared in a similar fashion as that described in Example 84 from Compound **192** (Structure **33** of Scheme VI, where R_1 = H, n =1) and trifluoroacetaldehyde ethyl hemiacetal. ^{1}H NMR (400 MHz, $CDCl_3$) 11.32 (br. s, 1H), 7.11 (s, 1H), 7.02 (s, 1H), 6.99 (s, 1H), 3.88 (q, 2H, J = 8.9), 3.47 (t, 2H, J = 5.6), 2.93 (t, 2H, J = 6.3), 2.03 (m, 2H).

EXAMPLE 89

4-Trifluoromethyl-6-propyl-6,7,8,9-tetrahydropyrido[2,3-*g*]quinolin-2(1*H*)-one (Compound **199**, Structure **34** of Scheme VI, where R_1 = H, R_2 = propyl, n = 1)

This compound was prepared in a similar fashion as that described in Example 84 from Compound **192** (Structure **33** of Scheme VI, where R_1 = H, n =1) and propionaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$) 11.23 (br. s, 1H), 7.07 (s, 1H), 6.99 (s, 1H), 6.78 (s, 1H), 3.34 (t, 2H, J = 5.6), 3.26 (t, 2H, J = 7.4), 2.88 (t, 2H, J = 6.3), 1.97 (m, 2H), 1.65 (m, 2H), 0.97 (t, 3H, J = 7.4).

EXAMPLE 90

4-Trifluoromethyl-6-ethyl-6,7,8,9-tetrahydropyrido[2,3-*g*]quinolin-2(1*H*)-one (Compound **200**, Structure **34** of Scheme VI, where R_1 = H, R_2 = ethyl, n = 1)

This compound was prepared in a similar fashion as that described in Example 84 from Compound **192** (Structure **33** of Scheme VI, where R_1 = H, n =1) and acetaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$) 11.23 (br. s, 1H), 7.07 (s, 1H), 7.00 (s, 1H), 6.82 (s, 1H), 3.39 (q, 2H, J = 7.1), 3.31 (t, 2H, J = 5.6), 2.88 (t, 2H, J = 6.4), 1.98 (m, 2H), 1.18 (t, 3H, J = 7.1).

EXAMPLE 91

4-Trifluoromethyl-6-cyclopropylmethyl-6,7,8,9-tetrahydropyrido[2,3-*g*]quinolin-2(1*H*)-one (Compound **201**, Structure **34** of Scheme VI, where R_1 = H, R_2 = cyclopropylmethyl, n = 1)

This compound was prepared in a similar fashion as that described in Example 84 from Compound **192** (Structure **33** of Scheme VI, where R_1 = H, n =1) and cyclopropanecarboxaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$) 11.44 (br. s, 1H), 7.06 (s, 1H), 7.00 (s, 1H), 6.92 (s, 1H), 3.40 (t, 2H, J = 5.6), 3.21 (d, 2H, J = 6.2), 2.90 (t, 2H, J = 6.3), 1.99 (m, 2H), 1.07 (m, 1H), 0.58 (m, 2H), 0.27 (m, 2H).

EXAMPLE 92

6,7-Dihydro-8,8-dimethyl-4-(trifluoromethyl)-8*H*-pyrano[3,2-*g*]quinolin-2(1*H*)-one (Compound **202**, Structure **39** of Scheme VII, where R_1 = R_3 = R_5 = H, R_2 = methyl, R_4 = trifluoromethyl)

General Method A: Substitution of a propargyl alcohol with a phenol. To a solution of the propargyl alcohol (1.16 equiv) and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, 1.3 equiv) in CH_3CN (0.5 mL/mmol) stirred at –5°C was added trifluoroacetic anhydride (1.16 equiv) and the flask was stirred for 40 min. In a second flask, to a mixture of the phenol (1.0 equiv) and CuCl (0.01 equiv) in CH_3CN (0.8 mL/mmol) was added DBU (1.5 equiv) at 0°C. This solution was added *via* cannula to the first flask. The mixture was stirred at 0°C for 4 h, then allowed to warm to rt. The mixture was partitioned between EtOAc (10 mL/mmol) and water (5 mL/mmol) and the aqueous layer was extracted with EtOAc. The combined organic layers were washed sequentially with 1 N $NaHSO_4$ (5 mL/mmol), $NaHCO_3$ (5 mL/mmol) and brine (5 mL/mmol), dried over $MgSO_4$, filtered and concentrated. Flash chromatography affords the desired product as an oil.

1-Nitro-3-(1,1-dimethylprop-2-ynloxy)benzene (Compound **203**, Structure **36** of Scheme VII, where R_1 = R_3 = H, R_2 = methyl).

This compound was prepared by the above General Method A from 2-methyl-3-butyn-2-ol (0.976 g, 11.6 mmol) and 3-nitrophenol (1.39 g, 10.0 mmol) in 40% yield (0.76 g) after flash chromatography (hexanes:EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) 8.11 (t, J = 2.2, 1H), 7.86-7.96 (m, 1H), 7.48-7.55 (m, 1H), 7.43 (t, J = 8.1, 1H), 2.66 (s, 1H), 1.70 (s, 6H).

General Method B: Thermal cyclization of a propargyl phenyl ether to a 2*H*-chromene. A solution of the propargyl phenyl ether was heated in N,N-diethylaniline (1-2 M) at 195°C or reflux for 12-30 h, whereupon the dark brown solution was partitioned between EtOAc (10 mL/mmol) and 1N $NaHSO_4$ (5 mL/mmol). The aqueous layer was extracted with EtOAc (10 mL/mmol) and the combined organic layers were washed sequentially with 1N $NaHSO_4$ (10 mL/mmol) and brine (10 mL/mmol), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (EtOAc:hexanes) afforded the desired product.

2,2-Dimethyl-7-nitro-2*H*-chromene (Compound **204**, Structure **37** of Scheme VII, where $R_1 = R_3 = H$, R_2 = methyl).

This compound was prepared by the above General Method B from Compound **203** (0.703 g, 3.71 mmol) in 1.9 mL *N,N*-diethylaniline heated at 195°C for 14 h in 18% yield (130 mg) after flash chromatography (hexanes:EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) 7.71 (dd, J = 8.3, 2.2, 1H), 7.61 (d, J = 2.1, 1H), 7.07 (d, J = 8.3, 1H), 6.37 (d, J = 9.9, 1H), 5.82 (d, J = 9.9, 1H), 1.47 (s, 6H).

7-Amino-2,2-dimethyl-2*H*-chroman (Compound **205**, Structure **38** of Scheme VII, where $R_1 = R_3 = H$, R_2 = methyl).

A suspension of Compound **204** (124 mg, 0.655 mmol) and 10% Pd-C (6.2 mg, 5 wt %) in 1.3 mL EtOAc and 1.3 mL EtOH was stirred under an atmosphere of hydrogen for 16 h, whereupon the mixture was filtered through Celite and concentrated. Flash chromatography (hexanes:EtOAc 3:1) afforded 112 mg (97%) of Compound **205**. ^{1}H NMR

(400 MHz, $CDCl_3$) δ 6.83 (d, J = 8.0, 1H), 6.21 (dd, J = 8.0, 2.3, 1H), 6.14 (d, J = 2.2, 1H), 3.50 (v. broad s, 2H), 2.66 (t, J = 6.7, 2H), 1.76 (t, J = 6.7, 2H), 1.31 (s, 3H).

6,7-Dihydro-8,8-dimethyl-4-(trifluoromethyl)-8*H*-pyrano[3,2-*g*]quinolin-2(1*H*)-one (Compound **202**, Structure **39** of Scheme VII, where $R_1 = R_3 = R_5 = H$, R_2 = methyl, R_4 = trifluoromethyl).

A solution of Compound **205** (9 mg, 0.050 mmol) and 4,4,4-trifluoroacetoacetate (57 mg, 0.30 mmol) was heated at 190°C in a sealed tube for 20 h, whereupon the mixture was cooled and precipitated with hexanes. Flash chromatography (CH_2Cl_2:MeOH 92:8) afforded 4 mg of a brown solid. Final purification by HPLC (ODS semi-prep column, MeOH:water 7:3, 3 mL/min) afforded 1.1 mg (7%) of Compound **205**, a white film. ^{1}H NMR (400 MHz, acetone-d_6) 10.9 (broad s, 1H), 7.50 (s, 1H), 6.84 (s, 1H), 6.69 (s, 1H), 2.93 (t, J = 6.8, 2H), 1.91 (t, J = 6.8, 2H), 1.38 (s, 6H).

EXAMPLE 93

6,7-Dihydro-8,8,10-trimethyl-4-(trifluoromethyl)-8*H*-pyrano[3,2-*g*]quinolin-2(1*H*)-one (Compound **206**, Structure **39** of Scheme VII, where $R_1 = R_2$ = methyl, $R_3 = R_5 = H$, R_4 = trifluoromethyl)

1-Nitro-2-methyl-3-(1,1-dimethylprop-2-ynloxy)benzene (Compound **207**, Structure **36** of Scheme VII, where $R_1 = R_2$ = methyl, $R_3 = H$)

This compound was prepared by General Method A (EXAMPLE 92) from 2-methyl-3-butyn-2-ol (0.976 g, 11.6 mmol) and 2-methyl-3-nitrophenol (1.53 g, 10.0 mmol) in 61% (1.34 g) yield after flash chromatography (hexanes:EtOAc 11:1). ^{1}H NMR (400 MHz, $CDCl_3$) 7.72 (d, J = 7.9, 1H), 7.49 (d, J = 7.8, 1H), 7.22 (t, J = 8.0, 1H), 2.60 (s, 1H), 2.36 (s, 3H), 1.69 (s, 6H).

2,2,8-Trimethyl-7-nitro-2*H*-chromene (Compound **208**, Structure **37** of Scheme VII, where $R_1 = R_2$ = methyl, $R_3 = H$).

This compound was prepared by General Method B (EXAMPLE 92) from Compound **207** (0.415 g, 1.89 mmol) in 2 mL *N,N*-diethylaniline heated at 190°C for 16 h in 59% yield (59%) after flash chromatography (hexanes:EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) 7.39 (d, J = 8.2, 1H), 6.91 (d, J = 8.2, 1H), 6.33 (d, J = 9.8, 1H), 5.78 (d, J = 9.8, 1H), 2.36 (s, 3H), 1.46 (s, 6H).

7-Amino-2,2,8-trimethyl-2*H*-chroman (Compound **209**, Structure **38** of Scheme VII, where $R_1 = R_2$ = methyl, R_3 = H).

A suspension of Compound **208** (241 mg, 1.10 mmol) and 10% Pd-C (12 mg, 5 wt %) in 2.2 mL EtOAc and 2.2 mL EtOH was stirred under an atmosphere of hydrogen for 16 h, whereupon the mixture was filtered through Celite and concentrated. Flash chromatography (hexanes:EtOAc 3:1) afforded 210 mg (100%) of Compound **209**. ^{1}H NMR (400 MHz, $CDCl_3$) 6.72 (d, J = 8.0, 1H), 6.24 (d, J = 8.0, 1H), 3.48 (broad s, 2H), 2.68 (t, J = 6.8, 2H), 2.01 (s, 3H), 1.74 (t, J = 6.8, 2H), 1.31 (s, 6H).

6,7-Dihydro-8,8,10-trimethyl-4-(trifluoromethyl)-8*H*-pyrano[3,2-*g*]quinolin-2(1*H*)-one (Compound **206**, Structure **39** of Scheme VII, where $R_1 = R_2$ = methyl, $R_3 = R_5$ = H, R_4 = trifluoromethyl).

A solution of Compound **209** (39 mg, 0.21 mmol) and 4,4,4-trifluoroacetoacetate (195 mg, 1.03 mmol) in 0.5 mL diphenyl ether was heated at 190°C in a sealed tube for 44 h, whereupon the mixture was cooled and precipitated with hexanes and filtered. Flash chromatography (CH_2Cl_2:ether) afforded 6.5 mg (10%) of Compound **209** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) 9.07 (broad s, 1H), 7.40 (s, 1H), 6.82 (s, 1H), 2.89 (t, J = 6.7, 2H), 2.26 (s, 3H), 1.86 (t, J = 6.7, 2H), 1.39 (s, 6H).

EXAMPLE 94

(±)-6,7-Dihydro-6-ethyl-4-methyl-8*H*-pyrano[3,2-*g*]quinolin-2(1*H*)-one (Compound **210**, Structure **39** of Scheme VII, where $R_1 = R_2 = R_5 = H$, R_3 = ethyl, R_4 = methyl)

1-Nitro-3-(pent-2-ynyloxy)benzene (Compound **211**, Structure **36** of Scheme VII, where $R_1 = R_2 = H$, R_3 = ethyl).

To a solution of 3-nitrophenol (7.5 g, 54 mmol) and K_2CO_3 (10.4 g, 75.6 mmol) in 27 mL DMF was added 2-pentynylmethanesulfonate (10.5 g, 65 mmol) and the mixture was stirred at rt for 18 h, whereupon the mixture was partitioned in ether:water (200 mL:200 mL). The aqueous layer was extracted with ether (2 x 100 mL) and the combined organic layers were washed sequentially with water (3 x 100 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated to afford 11.1 g (ca. 100%) of Compound **211** as a light brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) 7.80-7.90 (m, 2H), 7.40-7.50 (m, 1H), 7.27-7.35 (m, 1H), 4.76 (t, J = 2.1, 2H), 2.18-2.28 (m, 2H), 1.13 (t, J = 7.4, 3H).

1-Acetamido-3-(pent-2-ynyloxy)benzene (Compound **212**, Structure **36a** of Scheme VII, where R_3 = ethyl, $R_1 = R_2 = H$).

A suspension of Compound **211** (15.1 g, 73.5 mmol), Zn dust (325 mesh, 19.2 g, 294 mmol) and calcium chloride dihydrate (21.6 g, 147 mmol) in 300 mL 95% ethanol/water was heated at reflux for 20 h, whereupon the reaction mixture was filtered while hot through Celite and rinsed with 300 mL hot ethanol. The filtrate was concentrated to brown paste, which was partitioned between EtOAc (200 mL), water (200 mL) and 0.1 M HCl (25 mL). The aqueous layer was extracted with EtOAc (2 x 100 mL) and the combined organic layers were washed sequentially with water (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated to 12.6 g of a brown oil. This material was dissolved in 28 mL pyridine, cooled to 0°C, then DMAP (433 mg, 3.54 mmol) and acetic anhydride (8.68 g, 85.1 mmol) was added. After 20 min, the mixture was allowed to warm to rt and the mixture was stirred for 6 h. The reaction was quenched by the addition of 1 mL MeOH and the reaction mixture was partitioned between EtOAc (200 mL) and water (200 mL). The aqueous

layer was extracted with EtOAc (2 x 100 mL) and the combined organic layers were washed sequentially with 2N $NaHSO_4$ (3 x 100 mL), water (100 mL), $NaHCO_3$ (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (EtOAc:hexanes 3:2) afforded 9.6 g (62%) of Compound **212**. ^{1}H NMR (400 MHz, $CDCl_3$) 7.42 (broad s, 1H), 7.24 (broad s, 1H), 7.20 (t, J = 8.1, 1H), 7.06 (broad d, J = 8.1, 1H), 6.73 (dd, J = 8.1, 1.8, 1H), 4.64 (t, J = 2.0, 2H), 2.18-2.28 (m, 2H), 2.16 (s, 3H), 1.25 (t, J = 7.4, 3H).

7-Acetamido-4-ethyl-2*H*-chromane (Compound **213**, Structure **38a** of Scheme VII, where R_3 = ethyl, $R_1 = R_2$ = H).

A solution of Compound **212** (1.52 g, 7.00 mmol) in 3.5 mL *N,N*-diethylaniline was heated at reflux for 30 h, whereupon the brown solution was partitioned between EtOAc (60 mL) and 1N $NaHSO_4$ (30 mL). The aqueous layer was extracted with EtOAc (2 x 30 mL) and the combined organic layers were washed sequentially with $NaHSO_4$ (2 x 15 mL) brine (30 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (EtOAc:hexanes 1:1) afforded 0.44 g (29%) of Compound **213** as a light amber oil. This was carried on directly by treatment with 10% Pd-C (21 mg, 5 wt%) in 4.7 mL EtOAc and 4.7 mL EtOH and was stirred in 1 atm H_2 for 6 h, whereupon the mixture was filtered through Celite and concentrated to an oil. Flash chromatography (EtOAc:hexanes 1:1) afforded 0.42 g (100%, or 29% for the two-steps) of Compound **213**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.98-7.10 (m, 3H), 6.92 (s, 1H), 4.08-4.22 (m, 2H), 2.60-2.70 (m, 1H), 2.14 (s, 3H), 2.00-2.10 (m, 1H), 1.75-1.90 (m, 2H), 1.48-1.58 (m, 1H), 0.98 (t, J = 7.4, 3H).

7-Amino-4-ethylchroman (Compound **214**, Structure **38** of Scheme VII, where $R_1 = R_2$ = H, R_3 = ethyl).

A solution of Compound **213** (0.42 g, 1.9 mmol) in 3.8 mL 2N HCl was heated at reflux for 16 h, whereupon the solution was partitioned between EtOAc (40 mL) and saturated $NaHCO_3$ (20 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL) and the

combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (EtOAc:hexanes 1:1) afforded 0.30 g (90%) of Compound **214**. ^{1}H NMR (400 MHz, $CDCl_3$) 6.91 (d, J = 8.0, 1H), 6.24 (dd, J = 8.0, 2.4, 1H), 6.14 (d, J = 2.4, 1H), 4.05-4.19 (m, 2H), 3.52 (broad s, 2H), 2.55-2.65 (m, 1H), 1.95-2.05 (m, 1H), 1.70-1.85 (m, 2H), 1.42-1.52 (m, 1H), 0.97 (t, J = 7.4, 3H).

(±)-6,7-Dihydro-6-ethyl-4-methyl-8*H*-pyrano[3,2-*g*]quinolin-2(1*H*)-one (Compound **210**, Structure **39** of Scheme VII, where $R_1 = R_2 = R_5 = H$, R_3 = ethyl, R_4 = methyl).

To a solution of Compound **214** (53 mg, 0.30 mmol) and triethylamine (60 mg, 0.60 mmol) in 3 mL CH_2Cl_2 was added diketene (50 mg, 0.60 mmol) at 0°C. The solution was allowed to warm to rt and after 2 h was concentrated to an oil. Flash chromatography (EtOAc:hexanes 3:2) afforded 46 mg (59%) of 7-acetoacetamido-4-ethylchromàn, an oil. A portion of this material was carried on directly. A solution of 7-acetoacetamido-4-ethylchroman in 0.2 mL PPA (polyphosphoric acid) was heated at 100°C for 4 h. The mixture was precipitated with water and neutralized with 6N NaOH. The mixture was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (EtOAc:CH_2Cl_2 7:3) afforded 5 mg of a solid. Final purification by HPLC (ODS semi-prep column, MeOH:water 7:3, 3 mL/min) afforded 3.4 mg (36%) of Compound **210** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) 10.5 (broad s, 1H), 7.39 (s, 1H), 6.68 (s, 1H), 6.35 (s, 1H), 4.17-4.30 (m, 2H), 2.72-2.82 (m, 1H), 2.43 (s, 3H), 2.02-2.12 (m, 1H), 1.80-1.92 (m, 2H), 1.55-1.65 (m, 1H), 1.03 (t, J = 7.4, 3H).

EXAMPLE 95

(±)-7,8-Dihydro-8-ethyl-4-methyl-6*H*-pyrano[2,3-*f*]quinolin-2(1*H*)-one (Compound **215**, Structure **40** of Scheme VII, where $R_2 = R_5 = H$, R_3 = ethyl, R_4 = methyl)

This compound was isolated as a by-product from the preparation of Compound **210** described in Example 94. ^{1}H NMR (400 MHz, $CDCl_3$) 10.9 (s, 1H),7.21 (d, J = 8.4, 1H), 6.81

(d, J = 8.4, 1H), 6.37 (s, 1H), 4.17-4.30 (m, 2H), 2.67-2.77 (m, 1H), 2.65 (d, J = 0.9, 3H), 2.00-2.10 (m, 1H), 1.78-1.90
(m, 2H), 1.50-1.60 (m, 1H), 1.00 (t, J = 7.3, 3H).

EXAMPLE 96

(±)-6,7-Dihydro-6-ethyl-4-trifluoromethyl-8*H*-pyrano[3,2-*g*]quinolin-2(1*H*)-one (Compound **216**, Structure **39** of Scheme VII, where $R_1 = R_2 = R_5 = H$, R_3 = ethyl, R_4 = trifluoromethyl)

A solution of Compound **214** (Structure **38** of Scheme VII, where $R_1 = R_2 = H$, R_3 = ethyl) (14 mg, 0.079 mmol) and ethyl 4,4,4-trifluoroacetoacetate (17 mg, 0.095 mmol) in 0.8 mL benzene was heated at reflux for 14 h. The solution was concentrated and purified by flash chromatography (hexanes:EtOAc 3:2) to afford 21 mg of an oil. This was treated with PPA and heated at 100°C for 6 h. The dark brown sludge was partitioned between water (20 mL) and ethyl acetate (20 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (CH_2Cl_2:EtOAc 4:1) afforded 5.7 mg (29%) of a white solid. Final purification by HPLC (ODS semi-prep column, MeOH:water 7:3, 3 mL/min) afforded 3.4 mg (17%) of Compound **216** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) 11.2 (broad s 1H), 7.54 (s, 1H), 6.86 (s, 1H), 6.77 (s, 1H), 4.22-4.32 (m, 2H), 2.75-2.85 (m, 1H), 2.05-2.15 (m, 1H), 1.80-1.90 (m, 2H), 1.55-1.65 (m, 2H), 1.03 (t, *J* = 7.3, 3H).

EXAMPLE 97

(–)-6,7-Dihydro-6-ethyl-4-trifluoromethyl-8*H*-pyrano[3,2-*g*]quinolin-2(1*H*)-one (Compound **217**, Structure **39** of Scheme VII, where $R_1 = R_2 = R_5 = H$, R_3 = ethyl, R_4 = trifluoromethyl) and (+)-6,7-Dihydro-6-ethyl-4-trifluoromethyl-8*H*-pyrano[3,2-*g*]quinolin-2(1*H*)-one (Compound **218**, Structure **39** of Scheme VII, where $R_1 = R_2 = R_5 = H$, R_3 = ethyl, R_4 = trifluoromethyl)

Compound **216** was separated into its constitutive enantiomers *via* chiral HPLC on a semi-prep Chiralcel AD column (hexanes:isopropanol 97:3, 5.0 mL/min) to afford Compound

217 and Compound **218**. Data for Compound **217**: t_R 46.5 min (hexanes:isopropanol 97:3). Data for Compound **218**: t_R 58.3 min (hexanes:isopropanol 97:3).

EXAMPLE 98

(±)-6,7-Dihydro-6-ethyl-3-fluoro-4-trifluoromethyl-8*H*-pyrano[3,2-*g*]quinolin-2(1*H*)-one (Compound **219**, Structure **39** of Scheme VII, where $R_1 = R_2 = H$, R_3 = ethyl, R_4 = trifluoromethyl, $R_5 = F$)

A solution of Compound **214** (Structure **38** of Scheme VII, where $R_1 = R_2 = H$, R_3 = ethyl) (100 mg, 0.56 mmol) and ethyl 2,4,4,4-tetrafluoro-3,3-dihydroxybutanoate (185 mg, 0.84 mmol) was heated at 130°C for 20 h. The mixture was passed through a plug of silica gel (EtOAc) and concentrated to a brown oil. This oil was treated with 1.5 mL PPA and heated at 100°C for 6 h, then precipitated with cold water and neutralized with 6N NaOH. The mixture was extracted with EtOAc (3 x 25 mL) and the combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (CH_2Cl_2:EtOAc 4:1) afforded 70 mg (48%) of Compound **219** as a white solid. ^1H NMR (400 MHz, $CDCl_3$) 11.8 (broad s, 1H), 7.58 (s, 1H), 6.84 (s, 1H), 4.22-4.32 (m, 2H), 2.78-2.88 (m, 1H), 2.05-2.15 (m, 1H), 1.80-1.95 (m, 2H), 1.55-1.68 (m, 1H), 1.03 (t, J = 7.4, 3H).

EXAMPLE 99

(±)-6,7-Dihydro-6-ethyl-4-trifluoromethyl-1-methyl-8*H*-pyrano[3,2-*g*]quinolin-2(1*H*)-one (Compound **220**, Structure **41** of Scheme VII, where $R_1 = R_2 = R_5 = H$, R_3 = ethyl, R_4 = trifluoromethyl)

General Method: N-Methylation of a pyridone with sodium hydride and MeI. To a suspension of the pyridone (1 equiv) and NaH (60% mineral oil dispersion, 1.2-2.5 equiv) in THF (0.05 M) was added MeI (1.2-2.5 equiv). The mixture was stirred for 24 h and partitioned between CH_2Cl_2 and pH 7 phosphate buffer. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated and purified as indicated.

This compound was prepared according to the General Method described above from Compound **216** (Structure **39** of Scheme VII, where $R_1 = R_2 = R_5 = H$, R_3 = ethyl, R_4 = trifluoromethyl) (7.2 mg, 0.024 mmol), NaH (1.0 mg, 0.029) and MeI (2 μL, 0.029 mmol) in 51% yield (3.8 mg) after flash chromatography (CH_2Cl_2:MeOH 24:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (broad s, 1H), 6.90 (s, 1H), 6.81 (s, 1H), 4.24-4.36 (m, 2H), 3.65 (s, 3H), 2.75-2.85 (m, 1H), 2.07-2.17 (m, 1H), 1.80-1.95 (m, 2H), 1.58-1.68 (m, 1H), 1.04 (t, J = 7.4, 3H).

EXAMPLE 100

(±)-6,7-Dihydro-6-ethyl-3-fluoro-4-trifluoromethyl-1-methyl-8*H*-pyrano[3,2-*g*]quinolin-2(1*H*)-one (Compound **221**, Structure **41** of Scheme VII, where $R_1 = R_2 = H$, R_3 = ethyl, R_4 = trifluoromethyl, R_5 = F)

This compound was prepared according to General Method in Example **99** from Compound **219** (Structure **39** of Scheme VII, where $R_1 = R_2 = H$, R_3 = ethyl, R_4 = trifluoromethyl, R_5 = F) (11 mg, 0.034 mmol), NaH (3.0 mg, 0.085 mmol) and MeI (5.2 μL, 0.085 mmol) in 30% yield (3.4 mg) after purification by flash chromatography (CH_2Cl_2:MeOH 24:1). ^{1}H NMR (400 MHz, $CDCl_3$) 7.61 (s, 1H), 6.80 (s, 1H), 4.22-4.36 (m, 2H), 3.70 (s, 3H), 2.77-2.87 (m, 1H), 2.05-2.15 (m, 1H), 1.80-1.95 (m, 2H), 1.55-1.65 (m, 1H), 1.03 (t, J = 7.4, 3H).

EXAMPLE 101

(±)-6,7-Dihydro-6-ethyl-2,4-bis(trifluoromethyl)-8*H*-pyrano[3,2-*g*]quinoline (Compound **222**, Structure **42** of Scheme VII, where $R_1 = R_2 = H$, R_3 = ethyl)

To a solution of Compound **214** (Structure **38** of Scheme VII, where $R_1 = R_2 = H$, R_3 = ethyl) (30 mg, 0.17 mmol) and 1,1,1,5,5,5-hexafluoropentan-2,4-dione in 0.8 mL toluene was heated at 60°C for 18 h, whereupon *p*-toluensulfonic acid monohydrate (6.4 mg, 0.034 mmol) was added and the solution heated at 60°C for 6 h. The mixture was concentrated to an oil and purified by flash chromatography (CH_2Cl_2:hexanes 1:1) to afford 29 mg (49%) of Compound **222** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) 7.94 (s, 1H), 7.79 (s, 1H), 7.65

(s, 1H), 4.32-4.44 (m, 2H), 2.98-3.08 (m, 1H), 2.14-2.24 (m, 1H), 1.88-2.04 (m, 2H), 1.68-1.86 (m, 1H), 1.08 (t, J = 7.4, 3H).

EXAMPLE 102

6,8,8-Trimethyl-4-trifluoromethyl-8*H*-pyrano[3,2-*g*]coumarin (Compound **223**, Structure **47** of Scheme VIII, where R = methyl)

2,2-Dimethyl-7-hydroxy-4-chromanone (Compound **224**, Structure **44** of Scheme VIII).

1,3-Resorcinol (Structure **43** of Scheme VIII) (1g, 9.1 mmol) and 3,3-dimethylacrylic acid (909 mg, 9.1 mmol) were dissolved in trifluoroacetic acid (10 mL) and stirred at 80°C for 2 h. The reaction was made basic with 20% KOH to pH 7. The mixture was partitioned between EtOAc (50 mL) and water (50 mL). The aqueous was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed sequentially with water (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and concentrated. Flash chromatography (25% EtOAc/hexanes) afforded 1.5g (87%) of Compound **224**. ^{1}H NMR (400 MHz, acetone-d_6) 9.26 (bs, 1H), 7.66 (d, J = 8.7, 1H), 6.51 (dd, J = 8.7, 2.1, 1H), 6.33 (d, J = 2.1, 1H), 2.64 (s, 2H), 1.42 (s, 6H).

2,2,4-Trimethyl-4,7-dihydroxychroman (Compound **225**, Structure **45** of Scheme VIII, where R = methyl).

Compound **224** (250 mg, 1.3 mmol) was dissolved in diethyl ether and cooled to 0°C. Methyl magnesium bromide (3.0M, 2.6 mL, 7.8 mmol) was added slowly *via* syringe. The reaction was allowed to warm to room temperature. After 2 h the reaction was quenched with water and partitioned between EtOAc (25 mL) and water (25 mL). The aqueous was extracted with EtOAc (2 x 25 mL). The combined organic layers were washed sequentially with water (25 mL) and brine (25 mL), dried over Na_2SO_4, filtered and concentrated. Flash chromatography (30% EtOAc/hexanes) afforded 220 mg (81%) of Compound **225**. ^{1}H NMR

(400 MHz, acetone-d_6) 8.16 (s, 1H), 7.32 (d, J = 8.5, 1H), 6.4 (dd, J = 8.5, 2.5, 1H), 6.2 (d, J = 2.5, 1H), 3.7 (s, 1H), 2.03(s, 2H), 1.5 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H).

2,2,4-Trimethyl-7-hydroxy-2*H*-chromene (Compound **226**, Structure **46** of Scheme VIII, where R = methyl).

2,2,4-trimethyl-4,7-dihydroxychroman (**225**) (220 mg, 1.06 mmol), was dissolved in CH_2Cl_2 (5 mL) and treated with p-toluene sulfonic acid monohydrate (25 mg, 0.13 mmol). The resulting solution was stirred at rt for 2 h. The reaction was quenched with $NaHCO_3$ (sat.) to pH 7 and the mixture was partitioned between EtOAc (25 mL) and water (25 mL). The aqueous was extracted with EtOAc (2 x 25 mL). The combined organic layers were washed sequentially with water (25 mL) and brine (25 mL), dried over Na_2SO_4, filtered and concentrated. Flash chromatography (15% EtOAc/hexanes) afforded 135 mg (67%) of Compound **226**. ^{1}H NMR (400 MHz, acetone-d_6) 8.37 (s, 1H), 7.0 (dd, J = 8.4, 2.4, 1H), 6.26 (d, J = 2.4, 1H), 5.32 (s, 1H), 1.94 (s, 3H), 1.33 (s, 6H).

6,8,8-Trimethyl-4-trifluoromethyl-8*H*-pyrano[3,2-*g*]coumarin (Compound **223**, Structure **47** of Scheme VIII, where R = methyl).

Compound **226** (60 mg, 0.31 mmol) and ethyl-4,4,4-trifluoroacetoacetate (116 mg, 0.63 mmol) were dissolved in toluene and treated with $POCl_3$ (97 mg, 0.63 mmol) and stirred at 100°C for 8 h. The reaction was allowed to cool down to rt. The reaction was quenched slowly with dropwise addition of water and partitioned between EtOAc (25 mL) and water (25 mL). The aqueous was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed sequentially with water (25 mL) and brine (25 mL), dried over Na_2SO_4, filtered and concentrated. Flash chromatography (5% EtOAc/hexanes) afforded 40 mg (41%) of Compound **223**. ^{1}H NMR (400 MHz, acetone-d_6) 7.43 (s, 1H), 6.8 (s, 1H), 6.7 (s, 1H), 5.75 (s, 1H), 2.08 (s, 3H), 1.46 (s, 6H).

EXAMPLE 103

6-Ethyl-8,8-dimethyl-4-trifluoromethyl-8*H*-pyrano[3,2-*g*]coumarin (Compound **227**, Structure **47** of Scheme VIII, where R = ethyl)

4-Ethyl-2,2-dimethyl-7-hydroxy-2*H*-chromene (Compound **228**, Structure **46** of Scheme VIII, where R = ethyl).

Compound **224** (200 mg, 1.04 mmol) was dissolved in diethyl ether and cooled to 0°C. Ethyl magnesium bromide (3.0M, 1.7 mL, 5.2 mmol) was added slowly *via* syringe. The reaction was allowed to warm to room temperature. After 2 h the reaction was quenched with water and partitioned between EtOAc (25 mL) and water (25 mL). The aqueous was extracted with EtOAc (2 x 25 mL). The combined organic layers were washed sequentially with water (25 mL) and brine (25 mL), dried over Na_2SO_4, filtered and concentrated. The crude material was dissolved in CH_2Cl_2 (5 mL) and treated with p-toluene sulfonic acid monohydrate (25 mg, 0.13 mmol). The resulting solution was stirred at rt for 2 h. The reaction was quenched with $NaHCO_3$ (sat) to pH 7 and the mixture was partitioned between EtOAc (25 mL) and water (2 5 mL). The aqueous was extracted with EtOAc (2 x 25 mL). The combined organic layers were washed sequentially with water (25 mL) and brine (25 mL), dried over Na_2SO_4, filtered and concentrated. Flash chromatography (15% EtOAc/hexanes) afforded 220 mg (81%) of Compound **228**. ^{1}H NMR (400 MHz, acetone-d_6) 8.4 (bs, 1H), 7.15 (d, J = 8.5, 1H), 6.38 (dd, J = 8.5, 2.5, 1H), 6.28 (d, J = 2.5, 1H), 5.3 (s, 1H), 2.34 (q, J = 7.4, 2H), 1.11 (t, J = 7.4, 3H).

6-Ethyl-8,8-dimethyl-4-trifluoromethyl-8*H*-pyrano[3,2-*g*]coumarin (Compound **227**, Structure **47** of Scheme VIII, where R = ethyl).

Compound **228** (60 mg, 0.29 mmol) and ethyl-4,4,4-trifluoroacetoacetate (107 mg, 0.58 mmol) were dissolved in toluene and treated with $POCl_3$ (90 mg, 0.58 mmol) and stirred at 100°C for 8 h. The reaction was allowed to cool down to rt. The reaction was quenched slowly with dropwise addition of water and partitioned between EtOAc (25 mL) and water (25 mL). The aqueous was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed sequentially with water (25 mL) and brine (25 mL), dried over Na_2SO_4, filtered

and concentrated. Flash chromatography (5% EtOAc/hexanes) afforded 29 mg (31%) of Compound **227**. ^{1}H NMR (400 MHz, acetone-d_6) 7.48 (s, 1H), 6.81 (s, 1H), 6.69 (s, 1H), 5.74 (s, 1H), 2.48 (q, J = 7.4, 2H), 1.47 (s, 6H), 1.18 (t, J = 7.5, 3H).

EXAMPLE 104

(±)-5,6-Dihydro-6-hydroxymethyl-4-trifluoromethylpyrrolo[3,2-f]quinolin-2(1H)-one (Compound **228**, Structure **33a** of Scheme VI, where R_1 = hydroxymethyl, n = 0)

Compound **228** was prepared according to a similar procedure described in Example 81: ^{1}H NMR (500 MHz, acetone-d_6) 11.02 (bs, 1H), 7.39 (d, J = 8.8, 1H), 7.10 (d, J = 8.8, 1H), 7.01 (s, 1H), 3.94 (m, 2H), 3.86 (m, 1H), 3.55 (m, 1H), 1.42 (d, J = 6.1, 2H).

EXAMPLE 105

(±)-5,6-Dihydro-7-ethyl-6-hydroxymethyl-4-trifluoromethylpyrrolo[3,2-f]quinolin-2(1H)-one (Compound **229**, Structure **34a** of Scheme VI, where R_1 = hydroxymethyl, R_2 = ethyl, n = 0)

Compound **229** was prepared by ethylation of Compound **228**: ^{1}H NMR (500 MHz, $CDCl_3$) 11.71 (bs, 1H), 7.21 (d, J = 8.5, 1H), 7.15 (s, 1H), 6.80 (d, J = 8.5, 1H), 3.74 (m, 1H), 3.48 (m, 1H), 3.32 (m, 1H), 3.19 (m, 1H), 2.78 (m, 1H), 1.34 (d, J = 5.9, 2H), 1.11 (t, J = 6.5, 3H).

EXAMPLE 106

7,8-Dihydro-6-(2,2,2-trifluoroethyl)-4-trifluoromethylpyrrolo[2,3-g]quinolin-2(1H)-one (Compound **230**, Structure **34** of Scheme VI, where R_1 = H, R_2 = 2,2,2-trifluoroethyl, n = 0)

Compound **230** was prepared according to a similar procedure described in Example 81: ^{1}H NMR (500 MHz, acetone-d_6) 11.10 (bs, 1H), 7.32 (s, 1H), 6.82 (s, 1H), 6.80 (s, 1H), 4.13 (q, J = 10.0, 2H), 3.73 (t, J = 8.5, 1H), 3.22 (t, J = 8.5, 1H).

EXAMPLE 107

6-(2,2,2-Trifluoroethyl)-4-trifluoromethylpyrrolo[2,3-g]quinolin-2(1H)-one (Compound **231**, Structure **34b** of Scheme VI, where $R_1 = R_3 = H$, $R_2 = 2,2,2$-trifluoroethyl)

Compound **231** was prepared by oxidation of Compound 230: ^{1}H NMR (500 MHz, acetone-d_6) 10.93 (bs, 1H), 7.98 (s, 1H), 7.73 (s, 1H), 7.69 (d, J = 3.5, 1H), 6.87 (s, 1H), 6.71 (dd, J = 3.5 and 1.0, 1H), 5.31 (q, J = 9.0, 2H).

EXAMPLE 108

8-Chloro-6-(2,2,2-trifluoroethyl)-4-trifluoromethylpyrrolo[2,3-g]quinolin-2(1H)-one (Compound **232**, Structure **34b** of Scheme VI, where $R_1 = H$, $R_3 = Cl$, $R_2 = 2,2,2$-trifluoroethyl)

Compound **232** was prepared by chloronation of Compound 232: ^{1}H NMR (500 MHz, acetone-d_6) 11.04 (bs, 1H), 8.06 (s, 1H), 7.85 (s, 1H), 7.70 (s, 1H), 6.95 (s, 1H), 5.36 (q, J = 9.0, 2H).

EXAMPLE 109

5-Methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethylpyrrolo[3,2-f]quinolin-2(1H)-one (Compound **233**, Structure **19** of Scheme III, where R_4 = H, R_3 = methyl, R_5 = 2,2,2-trifluoroethyl)

This compound was isolated as an over oxidation product of Compound **150** (Structure **18** of Scheme III, where R_1 = R_2 = methyl) by the general oxidation procedure described in Example 49: ^{1}H NMR (500 MHz, DMSO-d_6) 12.2 (bs, 1H), 7.95 (d, J = 8.8, 1H), 7.27 (d, J = 8.8, 1H), 6.99 (s, 1H), 6.66 (s, 1H), 5.27 (q, J_{H-F} = 8.8, 2H), 2.53 (s, 3H).

EXAMPLE 110

6-Formyl-5-methyl-7-(2,2,2-trifluoroethyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **234**, Structure **19** of Scheme III, where R_4 = formyl, R_3 = methyl, R_5 = 2,2,2-trifluoroethyl)

This compound was prepared by the general oxidation procedure described in Example 49 from Compound **150** (Structure **18** of Scheme III, where R_1 = R_2 = methyl). ^{1}H NMR (500 MHz, DMSO-d_6) 11.9 (bs, 1H), 10.18 (s, 1H), 8.06 (d, J = 8.8, 1H), 7.52 (d, J = 8.8, 1H), 7.07 (s, 1H), 5.65 (q, J_{H-F} = 8.8, 2H), 2.62 (s, 3H).

EXAMPLE 111

5,6-Dimethyl-7-(2,2-difluorovinyl)-4-trifluoromethyl-7*H*-pyrrolo[3,2-*f*]quinolin-2(1*H*)-one (Compound **235**, Structure **19** of Scheme III, where R_4 = R_3 = methyl, R_5 = 2,2-difluorovinyl)

This compound was isolated as an over oxidation product of Compound **150** (Structure **18** of Scheme III, where R_1 = R_2 = methyl) by the general oxidation procedure described in Example 49: ^{1}H NMR (500 MHz, DMSO-d_6) 12.4 (bs, 1H), 7.76 (d, J = 8.8, 1H), 7.65 (d, J = 8.8, 1H), 7.16 (s, 1H), 5.05-5.00 (m, 1H), 2.45 (d, J = 0.9, 3H), 1.96 (s, 3H).

EXAMPLE 112

Steroid Receptor Activity

Utilizing the "cis-trans" or "co-transfection" assay described by Evans et al., Science, 240:889-95 (May 13, 1988), the disclosure of which is incorporated by reference herein , the compounds of the present invention were tested and found to have strong, specific activity as agonists, partial agonists and antagonists of AR. This assay is described in further detail in U.S. Patent Nos. 4,981,784 and 5,071,773, the disclosures of which are incorporated herein by reference.

The co-transfection assay provides a method for identifying functional agonists and partial agonists which mimic, or antagonists which inhibit, the effect of native hormones and quantifying their activity for responsive IR proteins. In this regard, the co-transfection assay mimics an *in vivo* system in the laboratory. Importantly, activity in the co-transfection assay correlates very well with known *in vivo* activity, such that the co-transfection assay functions as a qualitative and quantitative predictor of a tested compounds *in vivo* pharmacology. See, *e.g.*, T. Berger et al. 41 *J. Steroid Biochem. Molec. Biol.* 773 (1992), the disclosure of which is herein incorporated by reference.

In the co-transfection assay, a cloned cDNA for an IR (*e.g.*, human PR, AR or GR) under the control of a constitutive promoter (*e.g.*, the SV 40 promoter) is introduced by transfection (a procedure to induce cells to take up foreign genes) into a background cell substantially devoid of endogenous IRs. This introduced gene directs the recipient cells to make the IR protein of interest. A second gene is also introduced (co-transfected) into the same cells in conjunction with the IR gene. This second gene, comprising the cDNA for a reporter protein, such as firefly luciferase (LUC), controlled by an appropriate hormone responsive promoter containing a hormone response element (HRE). This reporter plasmid functions as a reporter for the transcription-modulating activity of the target IR. Thus, the reporter acts as a surrogate for the products (mRNA then protein) normally expressed by a gene under control of the target receptor and its native hormone.

The co-transfection assay can detect small molecule agonists or antagonists of target IRs. Exposing the transfected cells to an agonist ligand compound increases reporter activity in the transfected cells. This activity can be conveniently measured, *e.g.*, by increasing luciferase production, which reflects compound-dependent, IR-mediated increases in reporter transcription. A partial agonist's activity can be detected in a manner similar to that of the full agonist, except that the maximum measured activity, *e.g.*, luciferase production, is less than that of an agonist standard. For example, for AR, a partial agonist can be detected by measuring increased luciferase production, but the maximum effect at high concentration is less than the maximum effect for dihydrotestosterone. To detect antagonists, the co-transfection assay is carried out in the presence of a constant concentration of an agonist to the target IR (*e.g.*, progesterone for PR) known to induce a defined reporter signal. Increasing concentrations of a suspected antagonist will decrease the reporter signal (*e.g.*, luciferase production). The co-transfection assay is therefore useful to detect both agonists and antagonists of specific IRs. Furthermore, it determines not only whether a compound interacts with a particular IR, but whether this interaction mimics (agonizes) or blocks (antagonizes) the effects of the native regulatory molecules on target gene expression, as well as the specificity and strength of this interaction.

The activity of selected steroid receptor modulator compounds of the present invention were evaluated utilizing the co-transfection assay and in standard IR binding assays, according to the following illustrative Examples.

Co-transfection assay

CV-1 cells (African green monkey kidney fibroblasts) were cultured in the presence of Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% charcoal resin-stripped fetal bovine serum then transferred to 96-well microtiter plates one day prior to transfection.

To determine AR agonist and antagonist activity of the compounds of the present invention, the CV-1 cells were transiently transfected by calcium phosphate coprecipitation

according to the procedure of Berger et al., 41 *J. Steroid Biochem. Mol. Biol.*, 733 (1992) with the following plasmids: pShAR (5 ng/well), MTV-LUC reporter (100 ng/well), pRS-ß-Gal (50 ng/well) and filler DNA (pGEM; 45 ng/well). The receptor plasmid, pRShAR, contains the human AR under constitutive control of the SV-40 promoter, as more fully described in J.A. Simental et al., "Transcriptional activation and nuclear targeting signals of the human androgen receptor", 266 *J. Biol. Chem.*, 510 (1991).

The reporter plasmid, MTV-LUC, contains the cDNA for firefly luciferase (LUC) under control of the mouse mammary tumor virus (MTV) long terminal repeat, a conditional promoter containing an androgen response element. See *e.g.*, Berger et al. supra. In addition, pRS-ß-Gal, coding for constitutive expression of E. coli ß-galactosidase (ß-Gal), was included as an internal control for evaluation of transfection efficiency and compound toxicity.

Six hours after transfection, media was removed and the cells were washed with phosphate-buffered saline (PBS). Media containing reference compounds (*i.e.* progesterone as a PR agonist, mifepristone ((11β,17β)-11-[4-(dimethylamino)phenyl]-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one: RU486; Roussel Uclaf) as a PR antagonist; dihydrotestosterone (DHT; Sigma Chemical) as an AR agonist and 2-OH-flutamide (the active metabolite of 2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]pronanamide; Schering-Plough) as an AR antagonist; estradiol (Sigma) as an ER agonist and ICI 164,384 (N-butyl-3,17-dihydroxy-N-methyl-(7-α,17-β)-estra-1,3,5(10)-triene-7-undecanamide; ICI Americas) as an ER antagonist; dexamethasone (Sigma) as a GR agonist and RU486 as a GR antagonist; and aldosterone (Sigma) as a MR agonist and spironolactone ((7-α-[acetylthio]-17-α-hydroxy-3-oxopregn-4-ene-21-carboxylic acid γ-lactone; Sigma) as an MR antagonist) and/or the modulator compounds of the present invention in concentrations ranging from 10^{-12} to 10^{-5} M were added to the cells. Three to four replicates were used for each sample. Transfections and subsequent procedures were performed on a Biomek 1000 automated laboratory work station.

After 40 hours, the cells were washed with PBS, lysed with a Triton X-100-based buffer and assayed for LUC and ß-Gal activities using a luminometer or spectrophotometer, respectively. For each replicate, the normalized response (NR) was calculated as:

$$\text{LUC response/ß-Gal rate}$$

where ß-Gal rate = ß-Gal•$1x10^{-5}$/ß-Gal incubation time.

The mean and standard error of the mean (SEM) of the NR were calculated. Data was plotted as the response of the compound compared to the reference compounds over the range of the dose-response curve. For agonist experiments, the effective concentration that produced 50% of the maximum response (EC_{50}) was quantified. Agonist efficacy was a function (%) of LUC expression relative to the maximum LUC production by the reference agonist for PR, AR, ER, GR or MR. Antagonist activity was determined by testing the amount of LUC expression in the presence of a fixed amount of DHT as an AR agonist and progesterone as a PR agonist at the EC_{50} concentration. The concentration of test compound that inhibited 50% of LUC expression induced by the reference agonist was quantified (IC_{50}). In addition, the efficacy of antagonists was determined as a function (%) of maximal inhibition.

IR Binding assay

AR Binding: For the whole cell binding assay, COS-1 cells in 96-well microtiter plates containing DMEM-10% FBS were transfected as described above with the following plasmid DNA: pRShAR (2 ng/well), pRS-ß-Gal (50 ng/well) and pGEM (48 ng/well). Six hours after transfection, media was removed, the cells were washed with PBS and fresh media was added. The next day, the media was changed to DMEM-serum free to remove any endogenous ligand that might be complexed with the receptor in the cells.

After 24 hours in serum-free media, either a saturation analysis to determine the K_d for tritiated dihydrotestosterone (^{3}H-DHT) on human AR or a competitive binding assay to evaluate the ability of test compounds to compete with ^{3}H-DHT for AR was performed. For

the saturation analysis, media (DMEM-0.2% CA-FBS) containing ^{3}H-DHT (in concentrations ranging from 12 nM to 0.24 nM) in the absence (total binding) or presence (non-specific binding) of a 100-fold molar excess of unlabeled DHT were added to the cells. For the competitive binding assay, media containing 1 nM ^{3}H-DHT and test compounds in concentrations ranging from 10^{-10} to 10^{-6} M were added to the cells. Three replicates were used for each sample. After three hours at 37°C, an aliquot of the total binding media at each concentration of ^{3}H-DHT was removed to estimate the amount of free ^{3}H-DHT. The remaining media was removed, the cells were washed three times with PBS to remove unbound ligand and cells were lysed with a Triton X-100-based buffer. The lysates were assayed for amount of bound ^{3}H-DHT and ß-Gal activity using a scintillation counter or spectrophotometer, respectively.

For the saturation analyses, the difference between the total binding and the nonspecific binding, normalized by the ß-Gal rate, was defined as specific binding. The specific binding was evaluated by Scatchard analysis to determine the K_d for ^{3}H-DHT. See *e.g.*, D. Rodbard, "Mathematics and statistics of ligand assays: an illustrated guide" In: *J.* Langon and *J.J.* Clapp, eds., *Ligand Assay*, Masson Publishing U.S.A., Inc., New York, pp. 45-99, (1981), the disclosure of which is herein incorporated by reference. For the competition studies, the data was plotted as the amount of ^{3}H-DHT (% of control in the absence of test compound) remaining over the range of the dose-response curve for a given compound. The concentration of test compound that inhibited 50% of the amount of ^{3}H-DHT bound in the absence of competing ligand was quantified (IC_{50}) after log-logit transformation. The K_i values were determined by application of the Cheng-Prusoff equation to the IC_{50} values, where:

$$K_i = \frac{IC_{50}}{(1+[^3\text{H-DHT}])/K_d \text{ for } ^3\text{H-DHT}}$$

After correcting for non-specific binding, IC_{50} values were determined. The IC_{50} value is defined as the concentration of competing ligand needed to reduce specific binding by 50%. The IC_{50} value was determined graphically from a log-logit plot of the data. The K_i values were determined by application of the Cheng-Prusoff equation to the IC_{50} values, the labeled ligand concentration and the K_d of the labeled ligand.

The agonist, antagonist and binding activity assay results of selected androgen receptor modulator compounds of present invention and the standard reference compounds on AR, as well as the cross-reactivity of selected compounds on the PR, ER, MR and GR receptors, are shown in Tables 1-2 below. Efficacy is reported as the percent maximal response observed for each compound relative to the reference agonist and antagonist compounds indicated above. Also reported in Tables 1-2 for each compound is its antagonist potency or IC_{50} (which is the concentration (nM), required to reduce the maximal response by 50%), its agonist potency or EC_{50} (nM).

Table 1: Cotransfection and competitive binding data of selected androgen receptor modulator compounds of present invention and the reference agonist compound, dihydrotestosterone (DHT) and reference antagonists compound, 2-hydroxyflutamide (Flut) and Casodex (Cas), on AR.

Cmpd	AR Agonist CV-1 Cells		AR Antagonist CV-1 Cells		AR Binding
No.	Efficacy (%)	Potency (nM)	Efficacy (%)	Potency (nM)	K_i (nM)
104	78	183	50	1.8	15
105	57	32	na	na	45
106	108	12	na	na	45
108	66	24	na	na	6.7
109	97	13	na	na	1.2
110	106	21	na	na	21
112	na	na	75	10	119
113	na	na	65	316	529
114	na	na	81	6.6	81
119	94	2.5	na	na	2.6
120	117	4.5	na	na	12

Cmpd	AR Agonist CV-1 Cells		AR Antagonist CV-1 Cells		AR Binding
No.	Efficacy (%)	Potency (nM)	Efficacy (%)	Potency (nM)	K_i (nM)
121	97	43	na	na	7.6
122	59	34	na	na	21
123	104	1.4	na	na	14
125	121	38	na	na	1.3
126	53	11	na	na	2.3
127	66	25	na	na	6.3
129	79	1.6	na	na	3.2
132	70	4.8	na	na	21
134	70	4.2	na	na	6.8
137	77	145	na	na	107
141	46	86	44	34	97
144	na	na	53	23	1000
146	38	49	66	1	75
149	na	na	81	25	127
150	95	2.1	na	na	4.0
151	36	120	57	5.9	48
152	74	4.9	na	na	67
153	76	7.6	na	na	1.7
155	59	9.4	na	na	7.4
158	59	7.9	na	na	7.1
159	na	na	66	15	989
161	27	238	66	10	30
162	71	20	na	na	113
163	na	na	37	8.2	1000
166	96	24	na	na	17
172	89	19	na	na	12
173	41	138	56	1	80
175	na	na	78	11	239
177	na	na	98	790	31
178	24	21	48	50	900
179	91	1.3	na	na	4.1
182	na	an	81	13	1000
195	78	11	na	na	20
197	66	12	na	na	79
198	47	1.7	na	na	58
199	70	42	na	na	236

Cmpd	AR Agonist CV-1 Cells		AR Antagonist CV-1 Cells		AR Binding
No.	Efficacy (%)	Potency (nM)	Efficacy (%)	Potency (nM)	K_i (nM)
201	76	11	na	na	10
202	na	na	92	146	1000
206	na	na	90	175	1000
215	28	2070	77	17	47
216	55	11	28	4300	8.1
217	na	na	85	64	1000
218	82	10	na	na	4.1
220	na	na	67	23	1000
221	na	na	78	311	29
223	na	na	66	41	37
227	na	na	75	25	33
HO-Flut	na	na	83	25	34
Casodex	na	na	81	201	117
DHT	100	4.3	na	na	1.7

na = not active (*i.e.* efficacy of < 20 and potency of > 10,000); nd = not determined.

Pharmacological and Other Applications

As will be discernible to those skilled in the art, the androgen or progesterone receptor modulator compounds of the present invention can be readily utilized in pharmacological applications where AR or PR antagonist or agonist activity is desired and where it is desired to minimize cross reactivities with other steroid receptor related IRs. In vivo applications of the invention include administration of the disclosed compounds to mammalian subjects and in particular to humans.

The following Example provides illustrative pharmaceutical composition formulations:

EXAMPLE 113

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
COMPOUND 153	140
Starch, dried	100
Magnesium stearate	10
Total	250 mg

The above ingredients are mixed and filled into hard gelatin capsules in 250 mg quantities.

A tablet is prepared using the ingredients below:

	Quantity (mg/tablet)
COMPOUND **153**	140
Cellulose, microcrystalline	200
Silicon dioxide, fumed	10
Stearic acid	10
Total	360 mg

The components are blended and compressed to form tablets each weighing 360 mg.

Tablets, each containing 60 mg of active ingredient, are made as follows:

	Quantity (mg/tablet)
COMPOUND **153**	60
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (PVP) (as 10% solution in water)	4
Sodium carboxymethyl starch (SCMS)	4.5
Magnesium stearate	0.5
Talc	1.0
Total	150 mg

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of PVP is mixed with the resultant powders, which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The SCMS, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve and then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Suppositories, each containing 225 mg of active ingredient, may be made as follows:

	Quantity (mg/suppository)
COMPOUND **153**	225
Saturated fatty acid glycerides	2,000
Total	2,225 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of normal 2 g capacity and allowed to cool.

An intravenous formulation may be prepared as follows:

	Quantity
COMPOUND **153**	100 mg
isotonic saline	1000 mL
glycerol	100 mL

The compound is dissolved in the glycerol and then the solution is slowly diluted with isotonic saline. The solution of the above ingredients is then administered intravenously at a rate of 1 mL per minute to a patient.

The present invention includes any combination of the various species and subgeneric groupings falling within the generic disclosure. This invention therefore includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

While in accordance with the patent statutes, description of the various embodiments and processing conditions have been provided, the scope of the invention is not to be limited thereto or thereby. Modifications and alterations of the present invention will be apparent to those skilled in the art without departing from the scope and spirit of the present invention.

Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims, rather than by the specific examples which have been presented by way of example.